STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

# Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns ID899

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

**Title:** Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns

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All authors read and commented on draft versions of the ERG report.

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| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| ACLSCT | autologous cultured limbal stem cell transplantation |
| AMT | amniotic membrane transplantation |
| BSC | best supportive care |
| BSE | best seeing eye |
| CD | cadaveric donor |
| CI | confidence interval |
| CLAL | conjunctive limbal allograft from a living relative or cadaveric donor |
| CLAU | conjunctival limbal autograft |
| CS | company submission |
| CSR | clinical study report |
| DALK | deep anterior lamellar keratoplasty |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EQ-5D | EuroQol-5 dimension |
| ERG | Evidence Review Group |
| HLSTM | case series studies providing the clinical data for Holoclar |
| HRQoL | health-related quality of life |
| ICER | incremental cost effectiveness ratio |
| ITT | intention to treat |
| KLAL | keratolimbal autograft |
| Lr-CLAL | conjunctival limbal allograft from a living related donor |
| LSCD | limbal stem cell deficiency |
| LSCT | limbal stem cell transplantation |
| LY | life year |
| NICE | National Institute for Health and Care Excellence |
| OS | ocular surface |
| PAS | Patient Access Scheme |
| PKP | penetrating keratoplasty |
| QALY | quality adjusted life year |
| RCT | randomised controlled trial |
| SA | sensitivity analysis |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SLET | simple limbal epithelial transplantation |
| STA | single technology appraisal |
| SmPC | summary of product characteristics |
| TRAE | treatment-related adverse event |
| UCVA | uncorrected visual acuity |
| VA | visual acuity |
| WSE | worst seeing eye |

# 1 SUMMARY

## 1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE by Chiesi UK Ltd to support the use of a specific type of ex vivo expanded autologous human corneal epithelial cells, Holoclar®, within the licensed marketing authorisation for the treatment of moderate to severe limbal stem cell deficiency (LSCD) due to ocular burns. For brevity, throughout this ERG report, the intervention is referred to as 'Holoclar'.

Holoclar has been licensed in Europe since February 2015 for the treatment of adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired visual acuity [VA]), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1-2mm$^2$ of undamaged limbus is required for biopsy. The marketing authorisation is conditional on the company providing the results of an on-going prospective, European, uncontrolled phase IV study known as HLSTM03 (or HOLOCORE). The company expects the study results to be available in 2020.

The main clinical evidence presented in the company submission (CS) comes from the HLSTM01 study, an unpublished, retrospective case series study of 104 patients who were treated with Holoclar in two Italian ophthalmology centres between 1998 and 2008.

## 1.2 Critique of the decision problem in the company submission

**Intervention**

The intervention discussed in the CS is Holoclar. Treatment with Holoclar requires cells to be taken from a biopsy of the patient's undamaged limbus and shipped from the treating hospital to the site of Holoclar manufacture (Italy) where the cells are cultured on a fibrin membrane and then frozen. When the date for surgery is set, the manufacturer ships Holoclar to the hospital where it is implanted in the patient's eye. The mechanism of action of Holoclar is the replacement of corneal epithelium and lost limbal stem cells in patients in which the limbus has been destroyed by ocular burns. During the corneal repair process, the administered stem cells are intended to partially multiply, differentiate and migrate to regenerate corneal epithelium, as well as maintaining a reservoir of stem cells that can continually regenerate the corneal epithelium.

Holoclar is a living tissue equivalent and consists of a transparent circular sheet of 300,000 to 1,200,000 viable autologous human corneal epithelial cells (79,000-316,000 cells/cm$^2$), including on average 3.5% (0.4 to 10%) limbal stem cells, and stem cell-derived transient amplifying and terminally differentiated cells, attached on a supportive 2.2cm diameter fibrin layer and maintained in the transport medium. Each sheet of product is sufficient for a single treatment. Holoclar is the first advanced therapy medicinal product (ATMP) containing stem cells to receive a Marketing Authorisation in Europe.

**Population**

The population described in the final scope issued by NICE is adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2mm$^2$ of undamaged limbus. This is the same as the population described in the conditional licence for Holoclar issued by the European Medicines Agency (EMA).

The key clinical evidence describing treatment with Holoclar presented in the CS is derived from a single case series study (HLSTM01). Only one of the patients included in the HLSTM01 case series study had both eyes treated with Holoclar.

The company estimates that a maximum of 121 patients are likely to be currently eligible for treatment with Holoclar in the NHS in England. In addition to the prevalent population, there are likely to be 13 patients every year who are eligible for treatment with Holoclar.

**Comparators**

In the final scope issued by NICE, for patients with **unilateral** LSCD, the comparators are listed as conjunctival limbal autograft and BSC only. Clinical advice to the ERG is that limbal epithelial stem cells allografts are also used in the UK to treat unilateral LSCD.

In the final scope issued by NICE, for people with **bilateral** LSCD, the comparators are conjunctival limbal autograft, limbal epithelial stem cell allografts and BSC. Clinical advice to the company and to the ERG is that in the UK, conjunctival limbal autograft is unlikely to be used to treat patients with bilateral LSCD.

The ERG agrees with the company that the available evidence describing the clinical effectiveness of the comparators should be viewed with considerable caution.

The ERG is aware of emerging transplant techniques that are currently being trialled in different treatment centres in the UK and in other countries to treat patients with moderate to severe LSCD due to ocular burns (e.g., simple limbal epithelial transplant [SLET]).

**Outcomes**

Clinical evidence for the efficacy of Holoclar is reported in the CS for the majority of the outcomes specified in the final scope issued by NICE: clinical parameters of LSCD including stability and transparency of the corneal epithelium and superficial corneal neovascularisation, symptoms of LSCD including pain, burning and photophobia, VA and adverse effects (AEs) of treatment. The outcomes from the HLSTM01 case series study are reported post-operatively at 12 months for all patients; for a small group of patients later data are also available. Health-related quality of life (HRQoL) data pertaining to Holoclar are not presented in the clinical effectiveness section of the CS.

**Other considerations**

According to the economic analysis section of the final scope issued by NICE, the cost effectiveness analysis should include consideration of the benefit in the best seeing and worst seeing eyes.

In the company's unilateral LSCD model, by definition, the worst seeing eye is treated. In the company's bilateral LSCD model, by definition, both eyes are treated.

### 1.2.1 Equality and End of Life considerations

It is the company's opinion that, if Holoclar were not made available in the NHS in England, then a significant equality issue would arise for patients with LSCD due to ocular burns that were incurred whilst serving in the armed forces. The company highlights that these patients are likely to also have experienced the loss of limbs or other life changing events or injuries, both physical and mental, over and above those experienced by the general population of patients with the same condition. The ERG does not consider this to be an equality or equity issue.

The company has not presented a case for Holoclar to be assessed against the NICE End of Life criteria.

## *1.3 Summary of the submitted clinical effectiveness evidence*

The company did not identify any randomised controlled trials (RCTs) comparing Holoclar with any treatment in patients with moderate to severe LSCD due to ocular burns. Consequently, the company presents the results of a case series study (HLSTM01); this study includes a substantial number of patients (n=104) with a rare disease. Supportive evidence is also provided from two other case series studies known as HLSTM02 (n=29) and HLSTM04 (n=15). None of these studies are published.

In the intention-to-treat (ITT) population of the HLSTM01 case series study, transplant success (defined as: composite endpoint of rate of patients with none or mild superficial corneal neovascularisation and none or trace epithelial defects) was reported in 75 cases (72.1%; 95% confidence interval [CI]: 62.5% to 80.5%). Results of the sensitivity analysis excluding missing data were similar (75.8%; 95% CI: 66.1% to 83.8%). A masked independent assessor evaluated the data that were available for each case at baseline and at 12 months (n=46); the results suggested that the treatment was a success in 31 out of 46 cases (67.4%).

Visual acuity (measured using the Snellen chart) was improved by at least one line in 49% of patients (95% CI: 39.4% to 58.6%) and in 83.3% of patients (95% CI: 66.1 to 100%) without stromal scarring (15/18). The number of patients with symptoms of LSCD (pain, blurring, and photophobia) decreased between baseline and 12 months post-surgery.

There were six serious AEs reported (three were fatal) after six transplantations (5.3%). None were considered to be treatment-related. After 19 transplantations, 22 adverse drug reactions (16.8%) were reported. Adverse events that may have been related to corticosteroid treatment included five cases of glaucoma and one case of gastritis. One case of glaucoma was considered by the company to be treatment-related.

The company's systematic review of evidence from comparator studies identified one randomised study of 20 patients with unilateral LSCD who were treated with conjunctival limbal autograft sourced from either a living relative or derived from a cadaver. The remaining studies identified were either case studies or case series studies. The company stated that it was inappropriate to pool data from any of the identified comparator studies and instead provided a narrative summary of the data described in the comparator studies.

## *1.4 Summary of the ERG's critique of the submitted clinical effectiveness evidence*

The company carried out a search to identify evidence for the clinical effectiveness of Holoclar and a search to identify evidence for the clinical effectiveness of comparator technologies. The ERG is satisfied with the company's search strategies and is not aware of any studies that should have been included in the systematic reviews.

The company did not identify any RCTs that compare the use of Holoclar with any other treatment. Instead, the company presents the results of a retrospective case series study with a descriptive, observational design (HLSTM01). Using data from the HLSTM01 case series study, the company reports p-values and performs hypothesis testing. The ERG considers that this approach to data analysis is inappropriate as the purpose of a case series study is only to describe data.

The ERG agrees that the company has made attempts to mitigate against potential biases in the HLSTM01 case series study e.g., by using a pre-specified protocol to select cases, partially blinding outcomes and by quantifying the number of missing patient cases and assessing the impact of missing data. Despite these attempts, the ERG considers the HLSTM01 to be a poor quality case series study.

The marketing authorisation for Holoclar issued by the EMA includes its use in patients with unilateral and bilateral LSCD. There is no clinical effectiveness evidence presented in the CS to support the use of Holoclar to treat both eyes in patients with moderate to severe LSCD.

The ERG agrees with the company that pooling of data from the comparator studies is not possible inappropriate due to high levels of parameter heterogeneity.

## *1.5 Summary of submitted cost effectiveness evidence*

The company developed two de novo economic models in Microsoft Excel to compare the cost effectiveness of a unilateral or bilateral Holoclar transplant with four comparators, conjunctival limbal autograft (CLAU), conjunctival limbal allograft from a living relative (Lr-CLAL), keratolimbal autograft (KLAL) and best supportive care (BSC). The models have two main structural elements; a decision tree component for the initial treatment that includes any biopsy and transplant attempts, and a Markov component to capture longer-term outcomes. There are five health states represented in the Markov element of the model; the first two are relevant for the first year post-transplant and represent whether treatment has been successful or has failed. Beyond the first year post-transplant, patients can either be in a stable health state, have a failed transplant and be managed by BSC or die of other causes. Both models follow the same structure with the addition of treatment of the second eye in the bilateral case and there is a 12-month delay between the transplants in each eye. The model time horizon is set at 50 years with annual cycles in the Markov element. The model perspective is that of the UK NHS. Outcomes are measured in quality adjusted life years (QALYs). Costs and utilities are discounted at an annual rate of 1.5%. Utility values are obtained from both a bespoke standard gamble stated preference exercise and a literature search. Resource use and costs are estimated based on information from the HLSTM01 case series study for Holoclar and the expected patient pathways for the comparators.

In the base case for unilateral disease, Holoclar is dominated by CLAU as it is less effective and more expensive; the opposite is true for the comparison with BSC, therefore Holoclar dominates BSC. Holoclar provides additional benefit over Lr-CLAL (+2.36 QALYs) at an increased cost of £16,988. The company's base case incremental cost effectiveness ratio (ICER) for Holoclar versus Lr-CLAL is £7,185 per QALY gained. Holoclar is also more effective

than KLAL (+2.29 QALYs) at an additional cost of £5,167, resulting in an ICER of £2,255 per QALY gained.

In the base case, for bilateral disease, Holoclar is dominated by CLAU and dominates BSC. Holoclar provides additional benefit over Lr-CLAL (+2.89 QALYs) at an increased cost of £35,986. The company's base case ICER for Holoclar versus Lr-CLAL is £12,438 per QALY gained. Holoclar is also more effective than KLAL (+2.69 QALYs) at an additional cost of £17,572, resulting in an ICER of £6,533 per QALY gained.

The company carried out a number of alternative scenario analyses for patients with unilateral and bilateral disease.

**Scenario analysis: unilateral disease**

Holoclar is dominated by CLAU for all scenarios except when the source of clinical evidence for CLAU is changed and either the utility decrement for disfigurement is removed (ICER=£488,615 per QALY gained) or the time horizon is restricted to 22 years (ICER=£167,201 per QALY gained). When the time horizon is restricted to 22 years and there is a change to the source of the KLAL transition probabilities, the size of the ICER per QALY gained for Holoclar versus KLAL increases (+£27,233); for Holoclar versus BSC, Holoclar no longer dominates BSC with an ICER of £5,743 per QALY gained. Removal of the disfigurement utility decrement has a big influence on the comparison of Holoclar versus Lr-CLAL for patients with unilateral disease as the ICER is increased by £27,891 per QALY gained. When the discount rate is increased from 1.5% to 3.5%, Holoclar no longer dominates BSC (ICER=£3,563 per QALY gained); similarly, the ICERs increase for Holoclar versus Lr-CLAL (£13,997 per QALY gained) and versus KLAL (£12,990 per QALY gained).

**Scenario analysis: bilateral disease**

When the sources used for the transition probabilities are changed for comparative interventions and the disfigurement utility decrement is removed, Holoclar is no longer dominated by CLAU (ICER=£486,145 per QALY gained). In this same scenario, for Holoclar versus Lr-CLAL, the ICER is decreased by £10,510 per QALY gained and increased for Holoclar versus KLAL (+£12,416 per QALY gained), and Holoclar continues to dominate BSC. Increasing the annual discount rate from 1.5% to 3.5% has the biggest impact on the comparison of Holoclar with Lr-CLAL (ICER=£34,817 per QALY gained) and BSC, which Holoclar no longer dominates (ICER=£6,708 per QALY gained).

## 1.6 Summary of the ERG's critique of cost effectiveness evidence

The ERG is satisfied with the company's systematic review of cost effectiveness evidence and considers that the submitted models were reasonably well constructed with no flaws in the algorithms used to generate base case results.

The company's clinical effectiveness estimate for Holoclar is derived from a single, retrospective, case series study. Despite the study investigators' attempts to mitigate bias, the study has methodological flaws. Furthermore, the effectiveness evidence for each of the comparators that are used in the economic models is based on pooled data from the company's systematic review of the literature. The ERG notes that this approach is not described in the clinical or economic sections of the CS; in the clinical section of the CS, the company stated that pooling the data was not appropriate due to significant parameter heterogeneity between studies. Consequently, whether robust methods have been used to pool the data is unknown. However, as the individual studies have very small sample sizes, the ERG considers it doubtful that selection of any one study will produce more robust results than the pooled analysis. The ERG considers that the weak evidence base from which the intervention and comparator effectiveness is drawn needs to be taken into account when assessing the robustness of the ICERs generated by the company models.

In addition, the ERG has some concerns about the comparators employed in the economic models. First, the ERG considers that, in line with the NICE scope, CLAU is a treatment option for patients with unilateral disease and should be considered in the same way as the other comparators. The company claims that there are patients who are unsuitable for CLAU and/or who are unwilling to undergo treatment with CLAU and/or who have had an unsuccessful CLAU transplant. Clinical advice to the ERG is that this subgroup of patients is not clinically recognised or sufficiently well established and that CLAU is a valid treatment option for patients with moderate to severe LSCD.

Second, for patients with bilateral disease who are considering treatment in both eyes, the ERG agrees with the company that CLAU is not a valid treatment option and should not be considered alongside the other comparators.

However, the company does not present clinical effectiveness evidence to support the use of Holoclar to treat both eyes or to support the assumption that treatment of the second eye is is as effective as treatment in the first eye. The ERG considers this assumption to be implausible. For example, for patients with bilateral disease, any repeat biopsies that are necessary (which can be up to six in total) would have to be taken from a damaged eye. The company does not provide sufficient detail regarding whether or not this is possible in clinical practice. As such,

the cost effectiveness results associated with bilateral treatment cannot be used to inform treatment decisions for this group of patients.

Furthermore, the ERG considers that there are four issues that have a major impact on the cost effectiveness results generated by the company model (i.e., HRQoL, the discount rate, the use of autologous serum eye drops and use of KLAL on failure with Lr-CLAL).

The ERG agrees with the company that there are no HRQoL data available for this group of patients; the company has not collected any HRQOL data and there no published HRQoL data available from other relevant studies. After consultation with clinical experts and reviewing the utility values used in other studies of eye related diseases, the ERG considers that the utility values associated with the different health states employed in the base case are implausibly low and suggests using higher values.

The ERG considers that the stipulated NICE criteria permitting the application of a 1.5% discount rate for costs and benefits have not been met as Holoclar does not extend life or affect a cure for terminal disease. In addition, there is considerable uncertainty surrounding the size of the HRQoL impairment of patients with LSCD and the ability of Holoclar to restore these patients to full health. The ERG therefore considers that the standard 3.5% discount rate for costs and benefits should be used.

The cost of autologous serum eye drops is the main driver of cost in the economic models for Holoclar versus Lr-CLAL, KLAL and BSC.

The ERG's clinical experts consider that if autologous serum eye drops are used post-operatively, then they will be used after all transplantations including Holoclar. In the base case, it is assumed that these eye drops are not used after treatment with Holoclar but are used after all other transplantations. The ERG has therefore modified this assumption in the models and assumed that autologous serum eye drops are included in the cost of Holoclar treatment. Given the comparative nature of cost effectiveness analysis, the addition of autologous serum eye drops to treatment with Holoclar or removal from the comparator interventions has the same effect.

Whether autologous serum eye drops are routinely used to treat patients with flare-ups in the NHS is unknown. In the models, the company assumes that two flare-ups per year are treated with autologous serum eye drops. For clarity, the ERG considers that the cost effectiveness results associated with a scenario that does not permit the routine use of autologous serum eye drops for flare-ups must also be presented.

The company assumes that patients only have one type of transplant which is a particular issue for Lr-CLAL where it is assumed a patient can only have one transplant in their lifetime.

The ERG considers this assumption to be particularly implausible. When Lr-CLAL fails either the relative who offered a first donation could offer a second or a cadaver donor could be used to enable the transplant procedure to be repeated. The ERG presents a scenario, for unilateral patients, where two attempts at Lr-CLAL can occur. Given the similarities in terms of costs and effectiveness of Lr-CLAL and KLAL, this scenario can represent either two donations from a living donor or a second transplant from a cadaver donor.

## *1.7 Summary of company's case for End of Life criteria being met*

The company has not presented a case for treatment with Holoclar to be considered under NICE's End of Life criteria.

## *1.8 ERG commentary on the robustness of evidence submitted by the company*

### 1.8.1 Strengths

**Clinical evidence**

- Good quality systematic reviews were conducted in a complex disease area
- 104 patients with a rare disease were included in the HLMST01 case series study
- The company has a record of the total number of patients treated with Holoclar and is confident that there is more clinical effectiveness data to support the use of Holoclar than is available for any of the individual comparators.

**Cost effectiveness evidence**

- The economic models were reasonably well constructed
- Where data were limited, the company went to great lengths to identify data that could be used in the economic models
- The company carried out a comprehensive range of deterministic sensitivity analysis and scenario analyses.

### 1.8.2 Weaknesses and areas of uncertainty

**Clinical evidence**

- The evidence used to support the clinical effectiveness of Holoclar is derived primarily from a retrospective, single, case series study. The study authors have attempted to mitigate bias, but methodological flaws remain
- There is no clinical effectiveness evidence presented in the CS to support using Holoclar to treat two eyes in patients with bilateral LSCD
- The data available for the clinical effectiveness of the comparator technologies are weak. The majority of studies are small and observational in design.

**Cost effectiveness evidence**

- There is no gold standard comparator to which Holoclar can be compared
- For patients with unilateral disease, the company's base case ICER demonstrates that Holoclar is not cost effective compared to CLAU
- The company does not present any clinical effectiveness evidence to support the use of Holoclar to treat both eyes in patients with bilateral LSCD. Therefore, the ERG does not consider the cost effectiveness results associated with the company's bilateral model to be informative.

## *1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG*

The ERG identified several fundamental issues that cast doubt on the cost effectiveness of Holoclar versus all comparators. The ERG applied changes to the company models to address the identified issues including:

- Using a more plausible utility decrement for disfigurement and alternative utility values for differing VA
- Applying a 3.5% annual discount rate for costs and benefits
- Using autologous serum eye drops post-operatively for all procedures
- Not using autologous serum eye drops for flare-ups
- Allowing a second transplant attempt following the failure of treatment with Lr-CLAL.

**Results in the unilateral model**

CLAU dominates Holoclar when all of the ERG's modifications are implemented (individually and in combination). For Holoclar versus Lr-CLAL, with two transplant attempts, the ICER is £152,590 per QALY gained (£179,066 in the no serum eye drops at flare-up scenario). For Holoclar versus KLAL, the ICER is £33,473 per QALY gained (£60,996 in the no serum eye drops at flare-up scenario). For Holoclar versus BSC, the ICER is £8,155 per QALY gained (£35,489 in the no serum eye drops at flare-up scenario).

**Results in the bilateral model**

Application of the ERG's changes to utility values, discount rate and modifications to the use of autologous serum eye drops resulted in ICERs for Holoclar versus Lr-CLAL of £67,219 per QALY gained (£111,654 in the no serum eye drops at flare-up scenario). For Holoclar versus KLAL, the ICER is £75,457 per QALY gained (£122,468 in the no serum eye drops at flare-up scenario). For Holoclar versus BSC, the ICER is £14,288 per QALY gained (£50,973 in the no serum eye drops at flare-up scenario). However, the ERG considers that the ICERs generated by the bilateral LSCD model are of limited value due to i) the lack of evidence for the clinical

effectiveness of Holoclar to treat two eyes in the same patient and ii) the clinical implausibility of the company's assumption that Holoclar would be as effective in the second eye as in the first eye.

# 2 BACKGROUND

## 2.1 Critique of company's description of underlying health problem

Section 3.1 of the company submission (CS)[1] includes an overview of limbal stem cell deficiency (LSCD). Section 3.2 provides a description of the effect of moderate to severe LSCD due to ocular burns on patients, carers and society. Section 4.4 discusses the impact of vision on life expectancy. Key points from these sections are included as bulleted items in Box 1. The ERG considers that these points appropriately summarise the underlying health problems.

Box 1 Company overview of limbal stem cell deficiency

**Aetiology of moderate to severe LSCD**

- LSCD is characterised by a loss or deficiency of the progenitor stem cells located in the limbus that are vital for re-population of the corneal epithelium and to the barrier function of the limbus. This results in epithelial breakdown and recurrent or persistent epithelial defects, conjunctivalisation of the corneal surface with neovascularisation, chronic inflammation and corneal scarring. All of these contribute to loss of corneal transparency, potential visual loss, chronic pain and burning, photophobia and keratoplasty failure. In severe LSCD, part of the cornea, usually including the pupillary area, is covered by a thick fibrovascular pannus.[2] LSCD is an important cause of corneal blindness.[3]

- LCSD may result from direct injury to the limbal stem cells, destruction of the limbal stem cell niche, or both.[4] It can be caused by a wide variety of primary (inherited) and secondary (external) causes.[5-8] More rarely, there are unknown causes.[6,9]

- Secondary causes of LSCD often arise as a result of direct damage to the limbal stem cells.[6] This is most frequently associated with the sequelae of thermal (sometimes referred to as physical) or chemical (acid or alkali) burns and may also arise as a result of direct instilled drugs, contact lens usage or some therapies.[6] For example, prolonged use of high dose topical mitomycin C application may be associated with a relatively high incidence of LSCD.[10]

**Epidemiology of moderate to severe LSCD**

- LSCD is most frequently seen associated with severe physical or chemical burns[4,6,7] and bilateral involvement (both eyes) is reported to affect 20-38% of patients presenting with chemical burns.[11,12] Chemical burns are typically caused by acid or alkali injury[7,11] with household cleaners containing sodium hydroxide being among the most common causes of alkali injury. Acidic injuries are less common than alkali injuries and typically cause less damage to the ocular surface.[7]

- The estimated prevalence of LSCD due to ocular burns in Europe is 0.3 per 10,000 people.[13] In the UK, the reported incidence of LSCD due to severe chemical corneal injury is 0.02 per 100,000 in patients who had a mean age at time of injury of 33.8 years (median 38.5 years, range 10-59 years).[14]

- A 2011 review of 28 case reports and series published over 13 years[15] examined data from 583 patients (597 eyes) from centres undertaking cultured limbal stem cell transplantation in Australia, Germany, India, Iran, Italy, Japan, Taiwan, UK, and USA. In the studies reviewed, 75% of LSCD cases were caused by physical or chemical burns. In addition, the majority of patients were young males, who were treated for burns. A 2015 study of 16 patients[16] also documented chemical burns (31%) as being the most common cause of LSCD.

- Chronic effects on the ocular system have been documented in people exposed to sulphur mustard, (a chemical warfare agent) during the Iran-Iraq war, with an incidence of approximately

1%.[17] It is not clear whether LSCD is a direct effect of sulphur mustard toxicity or whether LSCD gradually progresses to a severe form because of chronic inflammation.[17]

**Course of moderate to severe LSCD**

- LSCD is a severe and painful condition that can affect patients with varying degrees of extent and severity.[5,16] It can be unilateral or bilateral (affecting one eye or both eyes) and either partial or total (affecting part or all of the cornea).[5,16]

- Although partial LSCD may be limited to a few sectors of the cornea, central vision can still be compromised.[8] If the problem is bilateral, the patient may be effectively blind. Corneal blindness affects quality of life and is often associated with an increased economic burden.[3]

- In terms of health consequences for patients with LSCD, the associated ocular surface disease poses a difficult management problem.[18] The clinical signs of LSCD are conjunctivalisation of the cornea with associated goblet cells, intense vascularisation, chronic inflammation, recurrent epithelial defects and stromal scarring.[5] Intense inflammation can cause secondary problems like increased eye pressure, the development of glaucoma and death of the optic nerve ganglion cells.[3]

- From the patient's perspective, the eye has little or no vision, it is often cosmetically unsatisfactory, and it may be uncomfortable or painful.[9,18,19] The symptoms experienced include excessive pain, eye discomfort associated with ocular surface problems including severe irritation, discomfort, photophobia, tearing, blepharospasm, chronic inflammation and redness, and decreased vision.[9,19] Most patients will lose their vision during the course of the disease.

**Effects on patients, carers, families and society**

- Patients with moderate to severe LSCD and their families face serious social challenges. Directly and indirectly, visual impairment interferes with many daily activities. In the case of adults, the possibilities for gainful employment are severely limited due to being unable to meet the greater visual demands in work situations, as is their participation in many other activities. To this is often added a loss of social status and self-esteem. The physical limitations and psychosocial implications of visual impairment cannot be measured in exact monetary terms. Nevertheless, it is clear that they diminish the quality of life not only for visually impaired persons, but for their families as well.[20]

- The effect of LSCD on patients is further exemplified by patient testimonial. Two testimonials have been provided by patients matching the indication for Holoclar and who were treated with limbal stem cell transplantation. (CS, p55 to 56).

**Impact on life expectancy**

- Given the estimated prevalence of LSCD due to ocular burns (0.3 per 10,000 people in Europe)[13] there are no data examining the effects of this condition on life expectancy. However, regional and global average life expectancies and health life expectancy at birth for 2015 have been reported by the WHO.[20]

LSCD=limbal stem cell deficiency; WHO=World Health Organisation
Source: CS, Sections 3.1, 3.2 and 4.4

## *2.2 Summary and critique of the company's overview of current service provision*

### 2.2.1 Current management options

In Section 3.1.4 of the CS, the company discusses the current management options for patients with moderate to severe LSCD due to ocular burns. The options include supportive management, conservative surgical options and invasive surgical techniques. The company explains that the aim of treatment is to restore the ocular surface and achieve corneal clarity.

The ERG considers that the discussion provided by the company is detailed and comprehensive. The company provides a helpful table that summarises the management options discussed in Section 3.1.4 of the CS (see Table 1).

Table 1 Current management options for LSCD

| Supportive treatments | Conservative surgery | Limbal stem cell transplantation | |
|---|---|---|---|
| | | **Procedure** | **Features** |
| Autologous serum drops<br><br>Eye lubrication<br><br>Therapeutic soft contact lens<br><br>Therapeutic scleral lens | Corneal scraping<br><br>Amniotic membrane transplantation (AMT) | CLAU: conjunctival limbal autograft | • Autograft from a patient's healthy eye<br>• Unsuitable for bilateral LSCD<br>• Minimum 4-6mm$^2$ of limbal tissue superiorly and inferiorly (minimum 8-12mm$^2$ total) is dissected from the patients other healthy eye and transplanted using a conjunctiva carrier[21-23]<br>• No immunosuppression required<br>• Risk of inducing LSCD in donor eye[6,22] |
| | | CLAL: conjunctive limbal allograft from a living relative (Lr-CLAL) or cadaveric donor | • Allograft from living relative or cadaveric donor.<br>• Suitable for bilateral LSCD<br>• Minimum 4-6mm$^2$ of limbal tissue superiorly and inferiorly (minimum 8-12mm$^2$ total) is dissected from the donor eye and transplanted using a conjunctiva carrier<br>• Requires systemic immunosuppression[24]<br>• Risk of disease transmission and neoplasia[6]<br>• Risk of inducing LSCD in the donor eye[6,22] |
| | | KLAL: keratolimbal allograft | • Allograft from cadaveric donor<br>• Suitable for bilateral LSCD[25,26]<br>• Entire donor limbus can be transplanted using the cornea as carrier tissue[9]<br>• Requires systemic immunosuppression[24]<br>• Risk of disease transmission and neoplasia[6] |

AMT=amniotic membrane transplantation; CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; KLAL=keratolimbal allograft; LSCD=limbal stem cell deficiency
Source: CS, Table 9

The company explains that **supportive management** includes ocular surface lubrication to prevent epithelial adhesion to the tarsal conjunctiva and to reduce shear stress.

**Conservative surgical options** include corneal scraping and amniotic membrane transplantation (AMT). The aim of corneal scraping is to remove overgrown conjunctiva and allow corneal healing and encourage repopulation of corneal epithelial stem cells. More than one procedure may be needed as the conjunctival epithelium migrates more rapidly than the corneal epithelium.[6]

The role of AMT is to encourage the production and migration of any remaining limbal epithelial stem cells and to reduce inflammatory reactions.[27] The amniotic membrane supports the growth of a healthy epithelium and the recovery of the corneal surface, thereby improving visual acuity (VA) and reducing pain and photophobia.[6] The AMT procedure may be used after corneal scraping[6] or as an adjunct to limbal stem cell transplantation.[25,27-29] The company reports that the biological source of the membrane may have an impact on clinical outcomes[6]

and that there is a theoretical risk of disease transmission (hence serological screening is carried out prior to transplantation).[19]

**Invasive surgical procedures** encompass three limbal stem cell transplantation techniques: conjunctival limbal autograft (CLAU), conjunctive limbal allograft from a living relative or cadaveric donor (CLAL) and keratolimbal allograft (KLAL). The differences between the three transplant techniques are related to the source of the donor stem cells and the carrier tissue used to transfer stem cells (Table 1). The final treatment decision takes into account a number of factors, such as the extent of the LCSD (bilateral or unilateral), patient expectation and willingness to undergo the procedure, the risk to the healthy eye and the availability and willingness of a living related donor.

Adjunctive surgical procedures might be carried out with limbal stem cell transplantation procedures, for example, penetrating keratoplasty (PKP) or deep anterior lamellar keratoplasty (DALK), with or without cataract surgery.[25] Both PKP (a full-thickness corneal graft) and DALK (selective replacement of the anterior layer of the cornea that leaves an intact endothelium) are used as treatments for corneal stromal scarring.

The company points out (CS, p53) that the success of the transplantation procedure is dependent on the condition of the ocular surface and its environment. The ERG understands that patients may need to undergo procedures prior to transplantation surgery, including (but not limited to) eyelid reconstruction, management of glaucoma, management of inflammation, corneal replacement. The eye must be 'quiet' for at least 3 months prior to transplantation surgery.

### 2.2.2 Holoclar and its proposed place of treatment in the NHS

Holoclar is a living tissue equivalent and consists of a transparent circular sheet of 300,000 to 1,200,000 viable autologous human corneal epithelial cells (79,000-316,000 cells/cm$^2$), including on average 3.5% (0.4 to 10%) limbal stem cells, and stem cell-derived transient amplifying and terminally differentiated cells, attached on a supportive 2.2cm diameter fibrin layer and maintained in the transport medium.[30] Each sheet of product is sufficient for a single treatment.[30]

Holoclar is a non-standard type of CLAU. Other non-standard types of CLAU include 'Simple Limbal Epithelial Treatment' (SLET). Treatment with Holoclar requires cells to be taken from a biopsy of the patient's limbus and shipped from the treating hospital to the site of Holoclar manufacture (Italy) where the cells are cultured on a fibrin membrane and then frozen. The manufacturer must receive the cells taken during the biopsy within 24 hours of acquisition from the patient. When the date for surgery is set, the manufacturer ships Holoclar to the hospital

where it is implanted in the patient's eye. Transplantation must take place within 36 hours of Holoclar being despatched by the manufacturer to the hospital.

The mechanism of action of Holoclar is the replacement of corneal epithelium and lost limbal stem cells in patients in which the limbus has been destroyed by ocular burns. During the corneal repair process, the administered stem cells are intended to partially multiply, differentiate and migrate to regenerate corneal epithelium, as well as maintaining a reservoir of stem cells that can continually regenerate the corneal epithelium. Holoclar is the first advanced therapy medicinal product (ATMP) containing stem cells to receive a Marketing Authorisation in Europe.

The company states (CS, p36) that in the UK, treatment with Holoclar will be carried out in two specialist ophthalmology centres (one in London and one in Newcastle). The company explains that limiting the number of treatment centres will ensure that the requisite surgical skills and experience in the treatment of the rare condition of LSCD will be developed and maintained. The company also states that Holoclar is to be commissioned by NHS England specialised services

The company states (CS, p58 and p59) that the introduction of Holoclar will not change the current treatment pathway within the NHS and considers Holoclar to be an alternative treatment option for the groups of patients listed in Table 2. The ERG notes that the European Medicines Agency (EMA) marketing authorisation[13] for Holoclar specifies its use in patients with moderate to severe LSCD due to ocular burns; there is no specific reference to Holoclar use in unilateral LSCD or bilateral LSCD.

Table 2 Patients with moderate to severe LSCD who would be treated with Holoclar

| **Patient subgroup** | |
|---|---|
| **Unilateral LSCD** | **Bilateral LSCD**<br>(Minimum of 1-2mm$^2$ of undamaged limbus) |
| Patients who are unsuitable for treatment with CLAU or who are unwilling to undergo CLAU because of concerns about damage to their donor eye | As an alternative to Lr-CLAL in patients without an available and/or willing live-related donor |
| Failed treatment with CLAU (once-only treatment) | Patients who are unsuitable for topical and systemic immunosuppression (immunosuppressive treatment is mandatory following Lr-CLAL and KLAL transplantation) |
| | Patients who require a successful treatment outcome beyond 3 to 5 years |

CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; KLAL=keratolimbal allograft; Lr-CLAL= CLAL from a live related donor; LSCD=limbal stem cell deficiency
Source: CS, p58

The ERG notes from Table 2 that the company is suggesting that for bilateral LSCD, the duration of successful treatment with conjunctival limbal allograft form a living relative (Lr-CLAL) and KLAL is between 3 and 5 years. Clinical advice to the ERG is that treatment

success varies between studies and also varies according to the use of immunosuppression treatment and the baseline characteristics of the patients.

### 2.2.3 NICE guidelines and NHS England policies

Section 3.5 of the CS describes the place of Holoclar in relation to NICE guidelines (Table 3), the NICE pathway for eye conditions (Table 3), the NHS Outcomes Framework and NHS England policies (Table 4). The ERG considers that the information provided by the company is appropriate and comprehensive.

Table 3 Company comments on the place of Holoclar within NICE guidelines and the NICE pathway

| NICE guideline | Summary of guideline | Company comments |
|---|---|---|
| IPG304[31] (2009) Corneal endothelial transplantation | Supports the use of corneal endothelial transplantation (the replacement of diseased corneal endothelium with a cadaveric donor endothelial graft) in patients with endothelial dysfunction. | For some patients with unilateral and partial bilateral LSCD, Holoclar would provide an alternative treatment option to corneal endothelial transplantation. |
| IPG216[31] (2007) Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium.* | The evidence for the safety and efficacy of tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium was not adequate for this procedure to be used without special arrangements for consent and for audit or research. Clinicians who wish to use the procedure should inform the clinical governance leads in their trust, ensure that patients understand the uncertainty about safety and efficacy, audit and review clinical outcomes of all patients undergoing the procedure. | Holoclar would provide a 'preferred' treatment alternative to tissue-cultured limbal stem cell allograft transplant for regrowth corneal epithelium for patients with moderate to severe LSCD. |
| NICE Pathway for Eye Conditions[32] | Describes the treatment pathway for patients with eye conditions. | The appropriate place for Holoclar within the NICE treatment pathway is in the Front of the eye' section in 'other corneal disease'. The NICE pathway for eye conditions is not well defined and that the majority of surgical treatments in use in the NHS have not been appraised by NICE. The introduction of Holoclar into the NHS would provide clear guidance in this area of the pathway. |

*IPG216 was considered for reassessment in 2010 but was not updated.
IPG=Interventional Procedures Guideline; LSCD=limbal stem cell deficiency
Source: CS, p61

**NHS Outcomes Framework**

The company is of the opinion that if Holoclar is recommended for use in the NHS, it would support the objectives of the NHS Outcomes Framework.[33] The introduction of Holoclar would enhance quality of life for people with long-term conditions thus improving 'Domain 2' and would support the 'overarching indicator 2' which is described as health-related quality of life (HRQoL) for people with long-term conditions.

**NHS England policies**

The company lists the NHS England policies relevant to treatment with Holoclar within the NHS and provides a commentary on the impact of the use of Holoclar on the policies (

Table 4).

Table 4 Company commentary on relevant NHS England policies

| NHS England policy | Company comments |
|---|---|
| NHS England (2014) Manual for prescribed specialised services 2013/14. Chapter 13. D12 - Adult specialist ophthalmology services.[34] | NHS England is the responsible commissioner for specialised ophthalmology services, and the Manual for Prescribed Services states that the NHS Commissioning Board (NHS England) commissions the following specialist services, including emergency care, for corneal disorders (severe anterior segment inflammation, high risk keratoplasty, endothelial keratoplasty, keratoprosthesis, collagen cross linking, excimer laser to treat corneal pathology), as well as oculoplastic surgery. NHS England has stated that the responsibility for commissioning ex vivo expanded autologous human corneal epithelial cells (Holoclar) sits with NHS England (not CCGs). |
| NHS England (2013) NHS standard contract for specialised ophthalmology (adult). Schedule 2 - the services - A. The specifications.[35] | The NHS standard contract for specialised ophthalmology services, states that current commissioned treatments by NHS England include 'Ocular surface reconstruction- keratolimbal allografts, ex vivo stem cell allografts, cultured oral mucosal epithelial transplant, conjunctival limbal autograft (living related also). |
| NHS England (2013) 2013/14 NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness (adults). Particulars, schedule 2- the services, a- service specification.[36] | The NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness (adults) is not expected to be impacted as it is not a direct comparator to ex vivo expanded autologous human corneal epithelial cells (Holoclar).<br>However, should improved success rates be seen in clinical practice compared with current treatment options, it is possible that the need for this intervention might be decreased from this patient group who may latterly be candidates for this treatment.<br>As such it is expected that a variation to the NHS specialised ophthalmology contract, or more likely the creation of a separate service specification and contract for ex vivo stem cell autografts will need to be created by NHS England to commission this service. |

CCG=clinical commissioning group
Source: CS, p62

## *2.3 Issues relating to current clinical practice*

The company makes the point (CS, p63) that all transplantation procedures (Holoclar, CLAU, KLAL) require essential pre-operative screening and post-operative follow-up procedures and that the costs of these procedures to the NHS are not reflected in the current codes for CLAU,

CLAL and KLAL. Based on clinical opinion, the company has listed the pre- and post-operative procedures associated with CLAU, CLAL and KLAL (CS, p64 to p66).

## 2.4 Innovation

The company puts forward the case that Holoclar is an innovative product (CS, p37). The company reports:

- The use of somatic stem cells taken from the intended patient offers major advantages (in comparison to embryonic stem cells) and allows for immediate therapeutic application.
- Holoclar offers several advantages over comparator technologies to transplant conjunctival-limbal or keratolimbal tissue in patients with LSCD, including lack of immunological rejection and hence the avoidance of immunosuppression, smaller amount of donor tissue required, the ability to treat both eyes and the possibility of retreatment if required. Holoclar may also offer a bridge to subsequent successful keratoplasty for some patients with LSCD complicated by deep stromal scarring, which in turn can further significantly improve VA.[13]
- Holoclar is the first ATMP containing stem cells to receive a Marketing Authorisation in Europe. To date there is no stem cell product with regulatory authority approval outside of the EU. This breakthrough in personalised, regenerative medicine responds to an unmet medical need for a rare and seriously debilitating orphan condition.
- Holoclar represents the first time that the ATMP Regulation (EC 1394/2007) has been successfully applied to a living cell-based product. However, as the development work for Holoclar was largely completed prior to the introduction of the ATMP Regulation, this required a novel regulatory approach reliant solely upon retrospective data, yet despite this, substantial numbers of patients for a rare condition (n=148) were included in the studies of Holoclar.[13] For all these reasons, the recommendation to approve Holoclar is considered one of the most significant milestones achieved by the EMA in the last 20 years.[37]
- Holoclar has been named one of four finalists shortlisted for an award in innovation and research – the UK Prix Galien Orphan Product award. A Prix Galien award is widely regarded as the highest distinction to bestow upon a pharmaceutical product.

## 2.5 Company's estimate of the number of patients eligible for treatment with Holoclar in the NHS

The company estimates that a maximum of 121 patients are likely to be currently eligible for treatment with Holoclar in the NHS in England (Table 5). The company also estimates that, in addition to the prevalent population, there are likely to be 13 new cases of severe chemical corneal injury each year (estimated incidence of 0.02 per 100,000).[14] The ERG considers that the company's estimates are reasonable.

Table 5 Company's estimates of the number of patients in England eligible for treatment with Holoclar

| Parameter | Number |
|---|---|
| Prevalence in EU of LSCD due to ocular burns[13] | 0.3 per 10,000 |
| UK population in 2014 = 64.6m[38] | 1938 |
| Number of people with LSCD in England (estimated)[38] | 1629 |
| 76% of people with LSCD are adults[38] | 1238 |
| 65% of adults with LSCD due to physical or chemical burns[39] | 805 |
| 20% of adults with LSCD due to physical or chemical burns with moderate to severe LSCD[39] | 161 |
| 75% of adults with LSCD due to physical or chemical burns with moderate to severe LSCD likely to receive surgical treatment[39] | 121 |

EU=European Union; LSCD=limbal stem cell deficiency; UK=United Kingdom.
Source: CS, p60 and p61

# 3 CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

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Table 6 summarises the decision problem described by the company in the CS[1] in relation to the final scope issued by NICE.[40] Each parameter is discussed in more detail in the text following the table.

Table 6 Final scope issued by NICE, company and ERG comments

| **NICE scope**<br>**Parameter and specification** | **Decision problem addressed in the company submission** | **ERG comment** |
|---|---|---|
| Population<br>Adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2mm$^2$ of undamaged limbus | As per final scope | Agree. However, the ERG notes that there is no clinical effectiveness evidence presented in the CS for the use of Holoclar in patients with bilateral LSCD |
| Intervention<br>Ex vivo expanded autologous human corneal epithelial cells containing stem cells | As per final scope | Agree |
| Comparator(s)<br>For people with unilateral LSCD<br>• conjunctival limbal autograft<br>• BSC<br>For people with bilateral LSCD<br>• conjunctival limbal autograft<br>• limbal epithelial stem cells allografts<br>• BSC | As per final scope | The ERG agrees with the company that limbal epithelial stem cells allograft is a relevant comparator for unilateral LSCD<br><br>The company presents evidence for conjunctival limbal autograft for people with bilateral LSCD but the ERG agrees with the company that this is not an appropriate comparator for this patient group |
| Outcomes<br>• clinical parameters of LSCD including stability and transparency of the corneal epithelium and superficial corneal neovascularisation<br>• symptoms of LSCD including pain, burning and photophobia<br>• VA (the affected eye)<br>• VA (the whole person)<br>• AEs<br>• HRQoL | As per final scope | The ERG notes that there are no HRQoL data presented in the clinical effectiveness section of the CS |
| Economic analysis<br>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye | As per final scope | Agree. However, the company does not explicitly present scenarios describing the treatment of best and worst seeing eyes |

| NICE scope<br>Parameter and specification | Decision problem addressed in the company submission | ERG comment |
|---|---|---|
| Other considerations<br>The costs and effects of BSC when given in combination with the intervention should be taken into account. Best supportive care includes topical steroids, ocular lubricants, bandage contact lenses, autologous serum eye drops, oral and/or topical vitamin C and oral tetracycline | **Issues related to equity or equality**<br>For Armed Forces personnel who acquire moderate to severe LSCD due to physical or chemical ocular burns sustained during service, e.g. due to explosive devices, the impact of LSCD in this group (unilaterally or bilaterally) may be further complicated by concomitant loss of limb and other life-threatening or life-changing injuries. As such, this group is disproportionately affected by physical disabilities, and other mental health sequelae, which differ to the general population of patients with moderate to severe LSCD due to physical or chemical ocular burns. A significant equality issue may therefore be created if Holoclar is not recommended for use within the NHS in England, contrary to the Armed Forces Covenant | The ERG does not consider this to be an equality or equity issue |

AE=adverse events; BSC=best supportive care; CS=company submission; ERG=Evidence Review Group; HRQoL=health related quality of life; LSCD=limbal stem cell deficiency; QALY=quality adjusted life year
Source: NICE Final scope and CS, Table 1

## 3.1 Holoclar clinical evidence

The ERG is aware that the treatment of LSCD due to ocular burns is a highly specialised area and notes that LSCD due to burns to the eyes is considered a rare condition by the EMA.[13] The number of patients treated each year is small and there is a limited number of treating clinics and clinicians in the UK NHS. There is no standard NHS treatment pathway and patient care may differ according to treatment centre.

There is no direct clinical evidence comparing Holoclar with any of the comparators listed in the final scope issued by NICE. The company provides clinical effectiveness evidence to support the clinical effectiveness of Holoclar from three unpublished case series studies HLSTM01,[41] HLSTM02[42] and HLSTM04.[43] In the CS, the company has focussed on the HLSTM01[41] study, a retrospective case series study of 104 patients with moderate to severe LSCD due to ocular burns who were treated with Holoclar in two Italian ophthalmology centres between 1998 and 2008. The stated duration of study follow-up is 12 months; however, there is a small group of patients for whom later data are available. The company also presents the results of five published, non-randomised, non-comparative studies[44-48] that describe the use of Holoclar in patients with moderate to severe LSCD; however, the majority of the data from the published studies is encompassed in the HLSTM01 case series study. The ERG notes that the evidence presented in the CS to support the clinical effectiveness of Holoclar is for the treatment of unilateral LSCD.

The company stated that it was inappropriate to carry out any direct or indirect clinical effectiveness treatment comparisons between Holoclar and any of the comparators listed in the final scope issued by NICE due to a lack of comparable clinical data. The company's systematic review did not identify any relevant randomised controlled trials (RCTs) that included the intervention specified in the final scope issued by NICE (see Table 1 for more details on comparators). The company's systematic review of evidence for the comparators

specified the final scope issued by NICE identified one randomised study[49] of 20 patients with unilateral LSCD who were treated with either CLAL or KLAL. However, the majority of available studies investigating the treatment of moderate to severe LSCD are largely observational and non-comparative. The company points out (CS, p112) that data from the studies are heterogeneous with differences in patient populations, culture methods, carrier substrates, length of follow-up and evaluation methods (see Section 3.4 of this ERG report for further discussion of the comparator studies).

The company also points out (CS, p112) that the majority of the clinical effectiveness evidence presented is only relevant to patients with unilateral moderate to severe LSCD.

The company has provided a narrative summary of the relevant comparator studies in the CS (CS, Table 12 and Table 14). The ERG agrees that given the data available, clinical effectiveness comparisons between Holoclar and the treatments specified in the final scope issued by NICE are not feasible. However, the company has carried out cost effectiveness comparisons.

## *3.2 Population*

The population described in the CS matches the population described in the final scope issued by NICE (i.e. adults with moderate to severe LSCD [defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA] unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1-2 $mm^2$ of undamaged limbus). This is the same population as described in the conditional licence for Holoclar issued by the EMA.[30]

*Treatment of unilateral and bilateral LSCD*

The company states that one of the major benefits of Holoclar is that it can be used bilaterally in patients that have at least 1-2$mm^2$ of healthy limbus in one eye. The company goes on to construct two separate economic models for the treatment of one eye (unilateral LSCD) and two eyes (bilateral LSCD). When used bilaterally, Holoclar is undertaken in both eyes at different times, 12 months apart. The company's labelling of the models is confusing. The company uses the term 'unilateral LSCD' to refer to the model that includes patients who have only one eye treated. However, the ERG recognises that, in the real world, there are patients with bilateral disease who would only ever have one eye treated. The company uses the term 'bilateral LSCD' to refer to the model that includes patients who have two eyes treated. Again, the ERG recognises that, in the real world, not all patients with bilateral LSCD will have both eyes treated.

During the clarification process, the ERG requested access to patient-level data from the HLSTM01 case series study asking the company to indicate whether patients had unilateral or bilateral LSCD. The company replied that, as this information was not recorded on the HLSTM01 Case Report Form, it was not possible to distinguish between unilateral and bilateral groups. However, the company was able to confirm that one patient had received Holoclar treatment in both eyes.

To use the clinical effectiveness data submitted by the company to support decision-making, it is necessary to make an assumption about the proportion of people within the HLSTM01 dataset who had unilateral and bilateral disease and then appraise the usefulness of the dataset to provide evidence for each of the indications individually. Advice from clinical experts and text in the CS suggest that in clinical practice the proportion of people with bilateral disease is about 10%.

The ERG considers that, although imperfect, it is acceptable to use the whole of the HLSTM01 case series study data to provide clinical effectiveness evidence for the unilateral use of Holoclar in patients with moderate to severe LSCD even though the population will likely consist of some patients with bilateral disease only having one eye treated. The use of the same dataset to support the bilateral use of Holoclar, however, is more much difficult to justify. Outcomes for bilateral patients receiving Holoclar in one or both eyes are impossible to determine from the HLSTM01 dataset provided by the company; for example, a single case study is not sufficient evidence to provide support for using Holoclar in both eyes for patients with moderate to severe LCSD.

In the absence of any clinical evidence to support using Holoclar bilaterally, the company has made the assumption that bilateral transplantation has the same success rate as unilateral transplantation. The ERG considers that this is unlikely to be the case for several reasons:

- Holoclar requires a biopsy of 1-2mm$^2$ of undamaged limbus for biopsy. In the bilateral case this has to be taken from a damaged eye. The company assumes that there is no difference in patient outcomes whether the limbal cells are taken from a damaged or undamaged eye. If this is true, it is unclear to the ERG why, during a unilateral intervention, the biopsy is performed on the healthy eye and not on the eye that is already damaged (but has some healthy limbus). This approach suggests to the ERG that there must be a clinical reason underlying the decision to take a biopsy from the healthy eye rather than from the damaged eye; whether this rationale is related to improved efficacy and patient outcomes is not known. The ERG speculates that it may be more difficult to locate and extract healthy limbal cells from a damaged eye than from a healthy eye.

- The company has assumed that the same number of biopsies can be taken from a healthy eye as from a damaged eye. Whether using a damaged or undamaged eye, the company states that there is a 10% chance that the first biopsy will fail. The company goes on to state that the Holoclar transplant itself can be carried out up to three times even if the first and second transplants fail. This means that a total of six biopsies could be required from a damaged eye that may only have 1-2mm$^2$ of undamaged limbus. The ERG does not consider this to be plausible. By default, that means that, even if the success rate per transplant is the same, overall efficacy of bilateral transplantation will be lower than the efficacy of unilateral transplantation simply due to the lower number of transplants that could be performed in patients undergoing bilateral intervention.

The company also states that multiple grafts can be grown from a single biopsy and that these can be frozen and used should the initial graft fail. This would potentially allow for only a single biopsy to be taken from a damaged eye and be used bilaterally if required. However, the company presents no evidence on the success rates with frozen and defrosted grafts nor does it indicate what the costs of this option would be. As such, the ERG considers that this approach should not be considered in the CS and the company rightly does not include it as an option in the economic model.

Given the clinical reasons to doubt the equal efficacy of using Holoclar unilaterally and bilaterally, and the absence of supportive clinical effectiveness evidence available, the ERG considers the assumption of equal efficacy to be unfounded.

## *3.3 Intervention*

Holoclar has been licensed in Europe since February 2015 for the treatment of adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns. A minimum of 1-2mm$^2$ of undamaged limbus is required for biopsy. The marketing authorisation is conditional on the company providing the results from an on-going prospective, European, uncontrolled phase IV study known as HLSTM03[50] (or HOLOCORE). The company expects the results of the study[50] to be available in 2020.

A regimen of post-implantation treatment is stipulated in the EMA marketing authorisation[13] for Holoclar. The regimen includes antibiotics (doxycycline or amoxicillin), prednisone, topical corticosteroids and dexamethasone eye-drops. Specific details are provided in the CS (p36) and in the SmPC.[30]

## 3.4 Comparators

In the final scope issued by NICE, the comparators for people with **unilateral** LSCD are listed as conjunctival limbal autograft and BSC only.

The ERG notes that in the final scope issued by NICE, limbal epithelial stem cells allograft is not listed a comparator for patients with unilateral LSCD. Clinical advice to the ERG is that limbal epithelial stem cells allografts (e.g., Lr-CLAL and KLAL) are used in the UK to treat unilateral LSCD.

The comparators for people with **bilateral** LSCD are conjunctival limbal autograft, limbal epithelial stem cell allografts and BSC.

After consultation with clinical experts, the company is of the opinion (CS, p112) that in the UK NHS, conjunctival limbal autograft (e.g., CLAU) is not used to treat patients with bilateral LSCD.[21,51] Clinical advice to the ERG is that patients with bilateral LSCD are unlikely to be treated with CLAU.

The company puts forward a number of caveats (CS, p20 and p112) when reviewing the evidence for the clinical effectiveness of the **comparators**:

- The available studies investigating the treatment of moderate to severe LSCD are largely observational and non-comparative
- Data from the studies are heterogeneous with differences in patient populations, culture methods, carrier substrates, length of follow-up and evaluation methods
- Data reported in the studies were collected over a period of 30 years; transplant methodology and BSC practice have evolved during that time
- The literature is likely to be open to several types of bias, including selection bias, assessment bias and publication bias.

The ERG agrees with the company that the available evidence describing the clinical effectiveness of the comparators should be viewed with considerable caution.

***3.5 The ERG is aware of emerging techniques that are currently being trialled in different treatment centres and in different countries to treat moderate to severe LSCD due to ocular burns. Examples of the emerging techniques include the Simple Limbal Epithelial Transplantation (SLET) procedure[52] and an ex-vivo expanded limbal stem cell transplantation method that is being trialled at the University of Newcastle.[53] Clinical advice to the ERG is that the SLET procedure can be used to treat patients in the NHS and, given the relative simplicity of the procedure, the use of SLET in the NHS is likely to increase. Publications relevant to SLET[52] and the work conducted at Newcastle[53] were excluded from the company's systematic review of comparator technologies on the grounds that they are outside of the scope because they do not address the efficacy, safety or impact on HRQoL of CLAU, CLAL or KLAL (CS, Appendix 4, p30 to p34). The ERG considers that SLET[52] and Newcastle's ex vivo expanded limbal stem cell transplantation system[53] are examples of non-standard CLAU and considers that both treatments are outside of the present scope as they are not routinely used in the UK NHS.***

***Outcomes***

Clinical evidence for the efficacy of Holoclar is reported in the CS for the majority of the outcomes specified in the final scope issued by NICE, i.e., clinical parameters of LSCD including stability and transparency of the corneal epithelium and superficial corneal neovascularisation, symptoms of LSCD including pain, burning and photophobia, VA and adverse effects (AEs) of treatment. The outcomes from the HLSTM01[41] case study are reported post-operatively at 12 months. Health-related quality of life data (HRQoL) data pertaining to Holoclar are not presented in the clinical effectiveness section of the CS.

## *3.6 Economic analysis*

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 50-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective. Costs and benefits were discounted at 1.5% per annum. The ERG is aware that the NICE Guide to the Methods of Technology Appraisal[54] states that an annual discount rate of 1.5% may be considered if the treatment restores people with severely impaired quality of life to full health for their remaining lifetime. However, the ERG considers that treatment with Holoclar does not meet this criterion (see Section 5.5.3 of this report) and that costs and benefits should therefore be discounted at the current NICE Reference Case value of 3.5% per annum.[54]

## *3.7 Subgroups*

According to the economic analysis section of the final scope issued by NICE, the cost effectiveness analysis should include consideration of the benefit in the best seeing and worst

seeing eyes. In the company's unilateral LSCD model, by definition, the worst seeing eye is treated. In the company's bilateral LSCD model, by definition, both eyes are treated. This means that the company has not directly considered the subgroups listed in the final scope.

## *3.8 Other considerations*

### 3.8.1 Equity considerations

In Table 1 and on pages 66 and 67 of the CS, the company discusses the Armed Forces Covenant which states that members of the armed forces community 'should face no disadvantage compared with other citizens in the provision of public and commercial services; and that special consideration is appropriate in some cases, especially for those who have given the most such as the injured or bereaved.'

The company highlights that people who have LSCD due to chemical or ocular burns incurred whilst serving in the armed forces are likely to also have experienced the loss of limbs or other life changing events or injuries, both physical and mental. The company argues that people from the armed forces with moderate to severe LSCD due to ocular burns are disproportionately affected by physical disability and resulting mental health problems compared to the general population of people with moderate to severe LSCD due to ocular burns. The company further argues that the restoration of eyesight has a greater impact on people with other disabilities than might be captured in the QALY calculation.

It is the company's opinion (CS, p67) that if Holoclar is not made available to the NHS in England, a significant equality issue would arise for patients with LSCD due ocular burns that were incurred whilst serving in the armed forces. The company highlights that these patients are likely to also have experienced the loss of limbs or other life changing events or injuries, both physical and mental, over and above those experienced by the general population of patients with the same condition. The ERG does not consider this to be an equality or equity issue.

# 4 CLINICAL EFFECTIVENESS

This section provides a structured summary and critique of the clinical effectiveness evidence submitted by the company in support of the use of Holoclar for the treatment of patients with moderate to severe LSCD due to ocular burns.

### 4.1.1 Systematic review methods

The company conducted a systematic review to identify studies of relevance to the appraisal under discussion. A summary of the systematic review methods employed by the company, with accompanying ERG comments, is presented in Table 7. Full details of the systematic review are provided in the CS (Section 4.1 and in Appendix 4). The company carried out a systematic review to identify evidence for the clinical effectiveness of Holoclar and a separate systematic review to identify evidence for the effectiveness of the comparator treatments.

Overall, the ERG is satisfied that the company's systematic review methods were of a good standard, and the objectives were relevant to the final scope issued by NICE and to the decision problem.

Table 7 Summary and ERG comment on the systematic review methods used by the company

| Review method | ERG comment |
|---|---|
| **Searching** | |
| • RCT and non-RCT data searches<br>• Databases searched included Medline, Medline in Process, Embase and CENTRAL (search strategies are described in Appendix 4 of the CS) from January 1989 to 4th January 2016<br>• Grey literature was searched for clinical studies and conference abstracts | • The ERG was able to replicate the searches<br>• The company searched the appropriate conference abstracts<br>• The ERG is confident that no relevant studies were missed |
| **Eligibility criteria** | |
| • Two independent assessors assessed study eligibility | • Use of two independent assessors improves the quality of reviews<br>• English and non-English language publications were considered by the company<br>• The ERG agrees with the company's rationale to simplify the inclusion criteria and limit to patients with a confirmed diagnosis of LSCD |
| **Data extraction** | |
| • Two independent assessors extracted data<br>• A pre-defined extraction form was used | • The company has not reported the method used to extract study data Quality assurance regarding data extraction is therefore uncertain<br>• The company contacted study authors for missing information |
| **Quality assessment and risk of bias** | |
| • Descriptive critical appraisal of all studies was undertaken using the NICE recommended method[55] | • Unclear if two independent assessors were employed<br>• No RCT evidence was presented in the CS for treatment with Holoclar. The Joanna Briggs appraisal tool for case series[56] was applied to the studies of Holoclar and to all the identified comparator studies. The ERG considers this approach to be appropriate except that one of the comparator studies was a randomised trial and should have been assessed with an appropriate tool |

LSCD=limbal stem cell deficiency; RCT=randomised controlled trial; CS=company submission
Source: CS, p68 to p71

### 4.1.2 Evidence synthesis

The company did not identify any relevant RCTs comparing Holoclar with any treatment in patients with moderate to severe LSCD due to ocular burns. The company identified five published[44-48] and three unpublished[41-43] non-RCTs (CS, p75).

The main focus of the CS is an unpublished case series study known as HLSTM01[41] with supporting evidence from two other related unpublished studies, HLSTM02[42] and HLSTM04.[43]

The company provides a narrative summary of all of the studies describing the clinical effectiveness of the comparators that are listed in the final scope issued by NICE (Table 12 and Table 14 of the CS).

The company's systematic review of comparator technologies identified 25 relevant studies. The company reports that 22 of the studies yield data pertinent to the outcomes measures specified in the final scope issued by NICE. The results of the systematic review of comparator technologies are discussed in section 4.7 of this ERG report.

The company was unable to carry out any direct or indirect comparisons between Holoclar and any of the comparators listed in the NICE scope due to a lack of comparable data across the identified studies.

## *4.2 Critique, analysis and interpretation of trials of the technology*

In response to the ERG's clarification request, the company explained the relationship between the five published studies[44-48] and the unpublished studies[41-43] of Holoclar presented in the CS (Table 8).

Details of the five published studies[44-48] are provided in Table 10 and Table 12 of the CS. A narrative summary of the results of the five published studies[44-48] is presented in Section 4.11.5 of the CS.

Table 8 Relationship between the five published studies of Holoclar and the three HLSTM case series studies

| Study ID | Number of patients | Relationship with HLSTM01/2/4 case series studies |
|---|---|---|
| Pellegrini 1997[46] | 2 | There is no overlap between the patient population reported in this pilot study and the patient populations reported in the HLSTM01, HLSTM02 and HLSTM04 studies |
| Rama 2001[47] | 18 | 6 of the 18 patients whose results are included in this publication were also included in the HLSTM01 study. There is no overlap between the patient population reported in Rama 2001 and the patient populations reported in the HLSTM02 and HLSTM04 studies |
| Rama 2010[48] | 112 | 93 of the 112 patients whose results are included in this publication were also included in the HLSTM01 study. There is no overlap between the patient population reported in Rama 2010 and the patient populations reported in the HLSTM02 and HLSTM04 studies |
| Marchini 2012[44] | 16 | There is no overlap between the patient population reported in this study and the patient populations reported in the HLSTM01, HLSTM02 and HLSTM04 studies |
| Pellegrini 2013[45] | 152 | There is almost complete overlap between the patient population reported in this study and the patient populations reported in the HLSTM01 and HLSTM02 studies. Out of the 152 patients included in the publication, 133 are included in the studies HLSTM01 and HLSTM02 studies. There is no overlap between the patient population reported in Pellegrini 2013 and the patient population reported in the HLSTM04 study |

ID= identification
Source: Company clarification response to QA2

### 4.2.1 Key studies presented in the company submission

The characteristics of the three unpublished case series studies of Holoclar (HLSTM01,[41] HLSTM02[42] and HLSTM04[43]) are described in Table 9. The main difference between the HLSTM01 case series study and the HLSTM02 case series study is related to treatment centre. The patients included in the HLSTM01 case series study were treated at two centres (in Milan and Rome); both centres used the same standard treatment protocol.

The patients included in the HLSTM02 case series study were treated at seven other centres in Italy.

The data included in the HLSTM04 case series study are derived from all patients who were treated with Holoclar from 2008 onwards (after the end of the period of data collection for HLSTM01 and HLSTM02). The 15 patients included in the HLSTM04 case series study were treated at three centres in Italy.

The company states (CS, p122) that 219 patients in total had been treated with Holoclar between 1998 and 2007 (HLSTM01 and HLSTM02). Of the 219 treated patients, data from 135 were available for inclusion in the HLSTM01 and the HLSTM02 case series studies. The company reports that data for the remaining 82 patients were not made available to the company by the investigators in the treatment centres. The ERG notes that 82 missing patients added to 135 included patients means that a total of 217 patients were treated (not 219). The company discusses the implications of the missing data in the CS but does not explain why the focus is on 219, rather than 217 patients (CS, p122 and p123). The ERG notes from the CS (CS, p126) that 106 patients were originally recruited to the HLSTM01 case series study; however only 104 patients were included in the ITT analysis. The ITT population was defined as patients who were treated with Holoclar and had a follow-up visit at least 6 months after the surgery.

Table 9 Characteristics of the HLSTM01, HLSTM02 and HLSTM04 case series studies

| Study | Study location and design | Intervention | Study population | Primary Outcomes | Secondary Outcomes | Duration of follow-up | Missing data |
|---|---|---|---|---|---|---|---|
| HLSTM01<br>Italy | Retrospective, uncontrolled, multicentre case-series non-randomised, | Ex vivo cultured ACLSCT Holoclar<br><br>(n=104) | Moderate to severe unilateral or bilateral LSCD due to ocular burns. A total of 106 patients who underwent at least one ACLSC transplantation were included in the study | Success based on: superficial corneal NV as 'none' or 'mild'; epithelial defects classified as 'none' (no staining) or 'tracing' (minimum staining) | Change in symptoms (pain, burning, photophobia), inflammation and VA. Number of ACLSCTs in each patient. Number of successful keratoplasties after ACLSCT. Evaluation of impression cytology: percentage of K3+, K3-, K12+, K12-, K19+, and K19- cells, and presence of caliciform cells | 12 Months | A sensitivity analysis was performed using the following two methods:<br>1) NOCB: Missing data at the endpoint visit were replaced by data available at the next closest visit;<br>2) Zero imputation: Missing data at the endpoint visit were considered a Failure (i.e. with neovascularisation). |
| HLSTM02<br>Italy | Retrospective, uncontrolled, multicentre case-series | Ex vivo cultured ACLSCT Holoclar<br>(n=29) | Moderate to severe unilateral or bilateral LSCD due to ocular burns. A total of 31 cases attended the pre-surgical visit: 29 underwent limbal biopsy and surgery for transplantation, and were included in the study | Number of subjects experiencing AEs and the number of AEs | Rate of ASCLCT recorded as success or failure based on investigator's judgement. Number of ASLSCTs in each patient. Number of successful keratoplasties after transplantation | ≥1 year | Secondary efficacy data were analysed as observed, without replacement for missing values. |
| HLSTM04<br>Italy | Retrospective, uncontrolled, multicentre case-series | Ex vivo cultured ACLSCT Holoclar<br>(n=15) | Moderate to severe unilateral or bilateral LSCD due to ocular burns. All patients started the treatment procedure (i.e. underwent biopsy) from 2008 to present | Safety and efficacy of ACLSCT in restoring normal and corneal epithelium | Safety of ACLSCT, including biopsy, surgical procedure and post-surgical treatments in terms of AEs, SAEs, ADRs and serious ADRs | ≥3 months | No imputation technique was applied to estimate missing values. |

ACLSC = autologous cultured limbal stem cell; ACLSCT=autologous cultured limbal stem cell transplantation; ADR=adverse drug reaction; AE=adverse event; LSCD=limbal stem cell deficiency; NOCB=next observation carried backward; NV=neovascularisation; SAE=serious adverse event; VA=visual acuity
Source: Clinical study report and CS, adapted from Table 11

This section of the ERG report focuses on the HLSTM01 case series study only. Details and outcomes of the HLSTM02 and HLSTM04 case series studies are included in Appendix 2 of this ERG report.

**Case series study design**

The main evidence presented in the CS is derived from non-randomised, non-controlled and retrospective case series studies. A case series study is a type of descriptive observational study where the main purpose is to follow a group of patients who have the same diagnosis or who are undergoing the same procedure over a certain period of time. Case series studies are not designed to test the hypothesis of treatment efficacy.[57]

Advantages of case series studies include high external validity if they enrol a wide range of patients with different characteristics and co-interventions and they are relatively inexpensive to run.

The disadvantages of case series studies are many. First, lack of randomisation and lack of comparison group mean that conclusions cannot be made about the effect of treatment on outcomes, as outcomes may be linked to treatment or to other patient characteristics. Lack of randomisation is a critical limitation as the investigators may favour their treatment of choice. Case series studies are susceptible to selection bias and measurement bias. Selection bias is present in case series studies when follow-up data are less likely to be collected from patients who are either performing better or worse than others, or if patients are not consecutively enrolled. Measurement bias is present in case series studies when different methods are used to measure the same outcome in different patients.

Kooistra[58] has proposed criteria for evaluating the design, analysis and reporting of case series studies and the ERG has applied the criteria to the HLSTM01 case series study. A description of the criteria can be found in Appendix 1.

The study question being addressed in the HLSTM01 case study is focussed and clearly set out. The inclusion and exclusion criteria are well defined and the intervention is described in detail. There is no information to indicate whether patients were included in the study consecutively; this means it is difficult to ascertain whether the inclusion period was short. The study also only explores efficacy and safety based outcomes; outcomes measuring patient satisfaction or mental wellbeing have not been included. A masked independent assessor assessed the primary efficacy outcome (i.e., treatment success or failure). However, one of the secondary outcomes, symptom resolution, was not assessed in this way. The baseline patient characteristics are described, but no explanation is provided for reasons why patients were lost to follow-up. The study authors explain the presence, direction and magnitude of

bias in detail (CS, Section 4.11.4). The authors do not draw absolute conclusions from their data; however, they make statements about the statistical significance of the outcomes and report p-values. Overall, the ERG considers that the HLSTM01 case series study is flawed as hypothesis testing has been carried out, there is lack of information about patient drop out and there are missing data.

## *4.3 Quality assessment of the HLSTM01 case series study*

The company appraised the HLSTM01 case series study using the Joanna Briggs Institute (JBI)[56] checklist for case series studies. The JBI checklist includes 10 items, each of which is scored as *yes*, *no*, *unclear* or *not applicable*. The company states (CS, p118) that in its assessment, a *yes* response was marked as 1, whilst all the other possible responses were marked as zero. In this way, a maximum of 10 points could be awarded per study. The company reports that the HLSTM01 study scored nine, suggesting a low risk of bias.

The ERG does not completely agree with the company's assessment (Table 10). The ERG did not have sufficient information to allow an assessment of one of the JBI criteria (whether the case series had consecutive inclusion of participants). The ERG considers that the company has not provided sufficient data on long-term follow-up and has carried out hypothesis testing. Hypothesis testing suggests that Holoclar is effective in spite of the aim of case series being to describe the data and not to form any conclusions. Therefore, the ERG is of the opinion that the case series study may have a greater risk of bias than the company claims.

Table 10 Company's assessment of the risk of bias for the HLSTM01 case series study with ERG comment

| JBI checklist criteria | Company assessment | ERG comment |
|---|---|---|
| Were there clear criteria for inclusion in the case series? | 1 | Agree |
| Was the condition measured in a standard, reliable way for all participants included in the case series? | 1 | Agree |
| Were valid methods used for identification of the condition for all participants included in the case series? | 1 | Agree |
| Did the case series have consecutive inclusion of participants? | 1 | The ERG is unclear how the company has assessed this criterion as sufficient information is not provided in the protocol or CSR to assess whether the case series studies have consecutively included participants or not |
| Did the case series have complete inclusion of participants? | 0 | Agree |
| Was there clear reporting of the demographics of the participants in the study? | 1 | Agree |
| Was there clear reporting of clinical information of the participants? | 1 | Agree |
| Were the outcomes or follow-up results of cases clearly reported? | 1 | The ERG agrees that outcomes of case series studies have been clearly reported, however sufficient long-term follow-up data have not been provided for the patients in the case series studies |
| Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | 1 | Agree |
| Was statistical analysis appropriate? | 1 | The ERG disagrees that the statistical analysis was appropriate for HLSTM01 as hypothesis testing has been carried out |
| Score | 9 | |

CSR=clinical study report; ERG=evidence review group
Source: CS, Appendix 4

## 4.4 Study characteristics

The study characteristics of the HLSTM01 case series studies are shown in Table 9. The ERG is aware that the number of patients included in the HLSTM01 study (n=104) is substantial, given the rarity of the condition. As noted in Section 4.2.1 of this ERG report, the HLSTM01 case series study was conducted in 106 patients. The 104 patients in the ITT population were those who had received treatment with Holoclar and had a control visit at least 6 months after transplantation.

The ERG notes that the duration of follow-up for the HLSTM01 and the HLSTM02 case series studies is 1 year.

## 4.5 Patient characteristics

The demographic characteristics of the patients in the HLSTM01 case series study are presented in Table 11. Clinical advice to the ERG is that the patients in the studies are representative of patients with moderate to severe LSCD who would be treated in the NHS.

Table 11 Patient baseline characteristics in the HLSTM01 case series study

| | **HLSTM01 N=104** |
|---|---|
| Mean age (standard deviation) | 46.8 (14.4) |
| Age range | 13.7 to 79.1 |
| Male n (%) | 80 (76.9) |
| Time from injury to treatment with Holoclar | 18.4 years |

Source: CSR for HLSTM01

## 4.6 Results from the HLSTM01 study

The results of the HLSTM01 case series studies discussed in this section are only for the outcomes specified in the final scope issued by NICE. All other study results are available in Section 4.11.5 of the CS. The ERG notes that all outcomes are reported after 1 year of follow-up. The company reports that HRQoL data were not collected.

The ERG notes that, for the HLSTM01 case series study, the company has presented p-values and conducted formal testing. However, this study is a case series study and the ERG considers that the results of any formal testing are invalid. For this reason, the ERG has not reported any p-values in this section.

The primary aim of the study was to determine the clinical efficacy of Holoclar. The ITT population included 104 patients with the per-protocol population including 99 patients.

The primary efficacy endpoint was rate of success of Holoclar transplantation based on stable corneal epithelium without significant recurrence of neo-vascularisation at 12 months post-intervention. In the ITT population (including missing data imputed as failure), success was reported in 75 patients (72.1%; 95% CI: 62.5 to 80.5%). Results of the sensitivity analysis excluding missing data were similar (75.8%; 95% CI: 66.1 to 83.8%). A masked independent assessor evaluated the results where data were available at both baseline and 12 months (n=46); the evaluation results suggested that the treatment was a success in 31 out of 46 cases (67.4%).

A secondary endpoint of the study is VA measured as both natural and best refracted using the Snellen chart and values expressed according to tenth scale. The results for VA suggest an improvement by at least one line in 49% of patients (95% CI: 39.4% to 58.6%) and in 83.3% (95% CI: 66.1 to 100%) of patients without stromal scarring (15/18).

The numbers of patients with symptoms at pre-surgical assessment and at 12 months post-surgery are displayed in Table 12. The results highlight that the number of patients with symptoms significantly decreased during the time between the pre-surgical assessment and 12 month post-surgery.

Table 12 Numbers of patients with symptoms at pre-surgical assessment and 12 months post-surgery

| Symptoms of LSCD | HLSTM01 (N=104) Pre-surgical assessment n (%) | HLSTM01 (N=104) 12 months post-surgery n (%) |
|---|---|---|
| Any symptoms | 40 (38.5) | 12 (11.5%) |
| Pain | 7 (6.7) | 0 (0)*^ |
| Burning | 30 (28.8) | 7 (6.7) |
| Photophobia | 35 (33.7) | 8 (7.7) |

LSCD=limbal stem cell deficiency;
Source: CS, p127
*based on 97 patients
^The value was corrected after the second committee meeting.

**Adverse events**

The company reports (CS, p160) the following AEs:

- Six serious adverse events (SAEs) (three were fatal) after six transplantation procedures (5.3%) all in patients who had had one transplant. None of the SAEs was considered to be treatment-related.
- There were 22 adverse drug reactions (16.8%) after 19 transplantations.
- There was one case of gastritis and five cases of glaucoma that were possibly related to treatment with corticosteroids. One case of glaucoma was considered to be treatment-related.

## *4.7 Company mitigation of potential bias in the three unpublished case series studies*

Exploration of study biases is very important, especially in studies of patients with rare diseases where there is limited published evidence. The company outlined the procedures that were undertaken in order to mitigate against potential bias in the unpublished Holoclar studies.

The company reports (CS, p122) that a protocol and statistical analysis plan (SAP) were generated prospectively. The protocol and SAP detailed how to collect and evaluate the retrospective data. The ERG considers that the protocol and SAP are of a good standard and confirms that all of outcomes and analyses were pre-specified.

The company re-evaluated some study outcomes using independent masked assessment. However, as only some of the efficacy outcomes (for some patients) were independently assessed, this raises concern over whether the other efficacy outcomes were influenced by the investigators in any way.

The company also addresses bias relating to the level of missing data present in the Holoclar studies. From the 219 patients included in the Holoclar studies, data are only available for 135 (61.6%) patients. The company explains that data for the remaining 82 patients were not available as the investigators declined an invitation to participate and provide the clinical data. As noted in Section 4.2.1 of this ERG report, the ERG is uncertain of the exact number of missing cases as the company's calculation (135 + 82) results in a total of 217 patients treated with Holoclar and not 219.

The company was unable to provide the reasons for the investigators' non-participation. The company states (clarification response A8) that 'declinations were proffered in written or verbal form or alternatively, no response to repeated invitations was also considered to be a declination. The reason for an investigator declining the invitation to participate in the HLSTM01 study was not requested nor required to be stated, only that the invitation had been declined.'

The company investigated whether the missing data could have an effect on the available evidence and invalidate it in any way. The company reports two of the published studies (Marchini[44] and Rama[47]) included 25 of the 82 missing patients. The company concludes that the results of the two published studies[44,47] are comparable to the results of the HLSTM01 and HLSTM02 case series studies; the ERG is concerned that the company's attempt to investigate the potential impact of missing data is insufficiently robust to support this conclusion. The ERG considers there is a risk that the presented results from 61.6% of the 219 patients treated with Holoclar (and included in the HLSTM01 and HLSTM02 case series studies) could be biased. Further assessment is needed to allow the effects of the missing data to be evaluated.

## *4.8 Company's systematic review of comparator studies*

The company reports (CS, p75) that 25 studies[11,23,26,27,49,59-81] were identified for inclusion in the systematic review of comparator interventions and that 22 of the studies[11,23,26,27,49,59,61-63,65-74,76-81] provided outcomes relevant to the final scope issued by NICE.

In the CS, the key tables relevant to the discussion of comparator studies are Table 12 (Published studies of comparator technologies identified by the systematic literature search) and Table 14 (Outcome measures for comparator technologies).

The ERG notes that in the 'conservative surgical options' category of Table 14 there appears to be a formatting error that has resulted in the omission of one, or possibly two studies.[59,71] The studies[59,71] both report outcomes for the use of AMT in a combined total of 20 patients. The ERG notes from Appendix 4 that the Anderson[59] and Kheirkhah[71] studies were listed in an earlier version of Table 14.

## *4.9 Assessment of risk of bias of the comparator studies*

The company has conducted a quality assessment of the studies included in Table 14 of the CS in which CLAU, CLAL, Lr-CLAL or KLAL were the interventions; the company did not quality assess the studies that described BSC treatments. The studies were appraised using the JBI[56] checklist for case series studies.

The company reports (CS, p118) that: i) seven of the 22 studies warranted a score of five or greater and ii) at least 12 of the 22 studies were awarded a score of 1 on the question of the outcomes or follow-up results being clearly reported. The ERG agrees with the company's assessment, but notes that two of the studies[74,79] were reported as abstracts only; abstracts do not always provide enough information to allow for a full assessment of a study. The ERG also notes that the study by Titiyal[49] is a randomised study and therefore should have been assessed using an appraisal tool appropriate for the critique of RCTs.

## *4.10 Characteristics of the comparator studies*

### 4.10.1 Conservative management (BSC)

The company did not identify any comparative studies of the use of BSC for the treatment of moderate to severe LSCD due to ocular burns (Table 13). The company identified one case report[76] that documented the use of therapeutic scleral lenses in LSCD not due to physical or chemical burns and one prospective case series study that described conjunctival epithelial scraping in four patients with chemically induced LSCD after keratoplasty.[61] The company also identified two case series studies of the use of AMT.[59,71]

### 4.10.2 Surgical interventions

The company states (CS, p117) that the evidence for the clinical effectiveness of CLAU, CLAL and KLAL is, for the most part, derived from non-randomised, non-controlled and retrospective case series studies. The company reports that one open label, randomised study[49] was identified. In this study, 20 patients with unilateral LSCD due to ocular burns were randomised to treatment with either CLAL or KLAL.

Table 13 Key characteristics of identified comparator studies

| Study ID and location | Intervention | Study design (as described in the CS) | Number of pts (total) | Follow-up | % pts with ocular burns | % pts unilateral | % pts bilateral | % pts achieving ocular stability | % pts with improvement in VA |
|---|---|---|---|---|---|---|---|---|---|
| **BSC** | | | | | | | | | |
| Schornack 2011[76]<br>USA | Therapeutic scleral lens | Single case<br>(USA) | 1 | 18 months | 0% | NR | NR | Integrity of ocular surface maintained | NR |
| Dua 1998[61]<br>UK | Conjunctival epithelial scraping | Prospective study<br>(UK) | 6 | Mean=7.5 months<br>(3 to 13 months) | 67% | NR | NR | NR | NR |
| Anderson 2001[59]<br>USA | AMT | Case series | 15 | Mean=25.8 months<br>(SD 2.5 months) | Unclear | NR | NR | * | * |
| Kheirkahn 2008 [62]<br>USA | AMT | Retrospective case review | 5 | Mean=16.8 months<br>(SD 10.8 months) | 100% | NR | NR | * | * |
| **Conjunctival limbal autograft CLAU** | | | | | | | | | |
| Dua 2000[62]<br>UK | CLAU | Case series | 6 | Mean=18.8 months<br>(14 to 31 months) | 50% | 100% | 0% | 100% | 100% |
| Kenyon 1989[70]<br>USA | CLAU | Case series | 26 | Mean=18 months<br>(2 to 45 months) | 85% | 65% | 35% | 95% | 43% |
| Moldovan 1999[74]<br>France | CLAU | Case series | 5 | 10 to 47 months | 100% | 100% | 0% | NR | 20%<br>(95% CI: 4% to 63%) |
| Rao 1999[23]<br>India | CLAU | Retrospective case study analysis | 16 | Mean=19.3<br>(SD 13.5 months)<br>(3 to 45 months) | 100% | 100% | 0% | 94%<br>(95% CI: 72% to 99%) | 69%<br>(95% CI: 42% to 87%) |
| **Limbal epithelial stem cells allografts (CLAL, KLAL)** | | | | | | | | | |
| Eslani 2015[63]<br>NR | KLAL | Retrospective review | 5 | N/A | 60% | NR | NR | NR | NR |
| Han 2011[65]<br>South Korea | KLAL | Retrospective case series | 22 | 47.9 months | 32% | 90% | 10% | 33% | 27% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Holland 1996[66]<br>USA | KLAL | Retrospective review | 21 | Mean=26.4 months<br>(6 to 63 months) | 38% | 0% | 100% | 72% | 60% |
| Huang 2011[67]<br>China | Lr-CLAL | Retrospective non-comparative case series | 17 | Mean=16.0 months<br>(12 to 26 months) | 100% | 29% | 71% | NR | 100%<br>(95% CI: 82% to 100%) |
| Ilari 2002[68]<br>UK | KLAL | Retrospective non-comparative case series | 20 | Mean=60 months<br>(15 to 96 months) | 40% | 85% | 15% | 21% | 44% |
| Maryuma-Hosoi 2006[72]<br>Japan | KLAL | Retrospective case series | 78 | Mean=46.6 months | 22% | 0% | 100% | 55%<br>(41% in ocular burns patients) | NR |
| Tsai 1994[80]<br>Taiwan | CLAL-CD | Case reports | 16 | Mean=18.5<br>(SD=5.4 months) | 31% | 0% | 100% | 63% | 81% |
| Tsubota 1995[81]<br>Japan | CLAL-CD | Case series | 9 | Mean=12.3 months<br>(2 to 17 months) | 33% | 0% | 100% | 56% | 100% |
| **More than one procedure used (CLAU, CLAL, KLAL)** | | | | | | | | | |
| Borderie 2003[60]<br>France | CLAU | Case series | 6 | Mean=36 months<br>(7 to 77 months) | 100% | 100% | 0% | NR | NR |
| | KLAL | | 5 | | 100% | 0% | 100% | NR | NR |
| Burcu 2014[11]<br>Turkey | CLAU | Retrospective analysis | 16 | Mean=77.2 months<br>(SD=35.1) | 100% | 100% | 0% | 87.5% (95% CI: 64.0% to 96.5%)** | 56%<br>(95% CI: 33% to 77%)<br>For total population |
| | CLAU + Lr-CLAL | | 4 | | Not included as a comparator in the CS | | | | |
| | Lr-CLAL | | 3 | | 100% | 100% | 0% | 100% | 56% (95% CI: 33% to 77%)<br>For total population |
| | CLAU+KLAL | | 1 | | Not included as a comparator in the CS | | | | |
| | KLAL | | 2 | | 100% | 100% | 0% | 50% | |
| Gomes 2003[27]<br>Brazil | AMT | Prospective, non-comparative interventional case series | 4 | Mean=19 months<br>(8 to 27 months) | Not included as a comparator in the CS | | | | |
| | CLAU+AMT | | 6 | | 100% | 100% | 0% | 83.3% (95% CI: 43.7% to 97.0%) | 87.5% (95% CI: 64.0% to 96.5%)<br>Total population (not broken out by subgroups) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Lr-CLAL | | 10 | | 100% | 0% | 100% | 60.0% (95% CI: 31.3% to 83.2%) | 87.5% (95% CI: 64.0% to 96.5%)<br>Total population (not broken out by subgroups) |
| Ivekovic 2005[69]<br>Croatia | CLAU | Case series | 6 | >1 year<br>(7 to 41 months) | 100% | 100% | 0% | CLAU: 100% (95% CI: 61% to 100%) | 100%<br>(95% CI: 61% to 100%) |
| | CLAU+AMT | | 4 | | 100% | 100% | 0% | CLAU + AMT: 100% (95% CI: 51.0% to 100%) | 100%<br>(95% CI: 51.0% to 100%) |
| Meallet 2003[73]<br>USA | CLAU+AMT | Retrospective, non-comparative, interventional small case series | 5 | 22 months<br>(11 to 48 months) | 60% | 100% | 0% | 100%<br>(95% CI: 56.6% to 100.0%) | 100%<br>(95% CI: 56.6% to 100.0%) |
| Miri 2010[26]<br>UK | CLAU | Retrospective consecutive cohort study | 12 | Mean=47 months<br>(12-119 months) | 50% total population | 100% | 0% | 100% | 100% |
| | Lr-CLAL | | 9 | Mean=32.6 months<br>(13 to 96 months) | | 0% | 100% | 89% | 89% |
| | CLAL-CD | | 6 | Mean=28.1 months (SD=36.9)<br>(22 to 96 months) | | 0% | 100% | 33% | 33% |
| Solomon 2002[77]<br>USA | KLAL+AMT | Retrospective non-comparative case series | 31 | Mean=34 months<br>(12 to 117.6) | 41% | NR | NR | NR | NR |
| Tan 1996[78]<br>UK | Lr-CLAL/CLAL-CD | Case series | 9 | 14.7 months<br>(4 to 24 months) | 11% | 0% | 100% | 78% | 44% |
| | CLAU | | 9 | 27.1 months<br>(10 weeks to 46 months) | 33% | 100% | 0% | 100% | 55% |
| Titiyal 2015[49]<br>India | Lr-CLAL | Open label randomised study | 10 | 6 to 22 months | 100% | 100% | 0% | 100%<br>(95% CI: 84% to 100%) | 80% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | KLAL | | 10 | 6 to 12 months | 100% | 100% | 0% | 100%<br>(95% CI: 84% to 100%) | 50% |
| Torres 2008[79]<br>Spain | CLAU | Case series | 58 | 20.8 months<br>(3 to 115 months) | 21% | 100% | 0% | 81% | NR |
| | CLAL-CD | | 14 | | 43% | 0% | 100% | 7% | NR |

AMT=amniotic membrane transplant; CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; CLAL-CD= conjunctival limbal allograft from a cadaveric donor; KLAL=keratolimbal allograft; Lr-CLAL=conjunctival limbal allograft from a living relative; NR=not reported; SD=standard; VA=visual acuity
* studies excluded from Table 14 of CS due to formatting error
* * An additional 5 patients underwent CLAU + lr-CLAL (n=4) and CLAU + KLAL (n=1). In these cases the initial CLAU procedure failed and a second transplant was required. With these cases taken into account, OS is achieved in 66.7%
Source: CS, Table 12 and Table 14 (The ERG has not included the 2 review papers[64,75] cited in Table 12 of the CS)

The company summarises the studies identified in the systematic review of comparator studies for CLAU, CLAL and KLAL (CS, p134) as follows:

- There is a greater body of published evidence for the use of CLAU, CLAL or KLAL than for conservative management, but this is also largely based on case series data and is very heterogeneous in terms of patient populations (causes of LSCD and degree of severity of LSCD at baseline). Most studies included patients with a range of causes of LSCD.
- In the majority of cases, unilateral LSCD was managed with CLAU;[11,23,26,27,60,62,69,70,73,74,78,79] in some case series studies[11,49,65,68] unilateral LSCD was treated with CLAL or KLAL.
- In all but one case, bilateral LSCD was treated with CLAL or KLAL.[26,27,60,65-68,72,78-81] One study[70] described the use of CLAU in in patients with bilateral LSCD; however, at the time of the study, the use of CLAU in patients with bilateral LSCD was considered experimental. Expert opinion to the company clearly indicates that CLAU is not used in the UK NHS to treat patients with bilateral LSCD and has not been undertaken in the UK by the experts consulted. The ERG agrees with the clinical advice given to the company that CLAU is not used in the UK NHS to treat bilateral LSCD.[21,51]
- In some case series studies, the authors did not report whether the patients had unilateral or bilateral LSCD.[63,77]
- There was a range of primary clinical outcomes reported, e.g. histology (epithelialisation), VA, ocular surface outcomes, symptom improvement (pain, inflammation etc.), neo-vascularisation and rejection (allograft). There is no single universally accepted standard endpoint for assessing clinical outcomes in LSCD.
- In some cases clinical outcomes were reported on an individual patient basis or else grouped rather than stratified by cause of LSCD. Due to the design of the case series and the small patient numbers, there was limited statistical analysis or the statistical analysis was not relevant to the endpoints of interest in this review.
- In some case series there was more than one intervention non-comparatively assessed (CLAU, CLAL, KLAL, CLAU+AMT, CLAL+AMT, CLAU/CLAL/KLAL followed by keratoplasty and finally CLAU+CLAL and CLAU+KLAL).
- The impact of treatment on HRQoL was not assessed in any of the studies identified in the systematic review.

The company also reports (CS, p116) that there was variation in the duration of follow-up between studies. For CLAU and CLAL/KLAL, follow-up ranged from a mean of 12 months[69,81] to 9.4 years.[66] The ERG agrees with the company that there is considerable variation in the mean duration of follow-up; however, the ERG considers that the maximum mean length of follow-up is 77.2 months (not 9.4 years).[11]

The company cautions (CS, p112) that the results of the studies included in the systematic review of comparator technologies should be interpreted with caution due to the weak study designs and the heterogeneity in patient populations and interventions. The company discusses (Table 14) issues relevant to the studies including the patient populations, surgical technique and clinical endpoints in the included studies. The ERG agrees with the company's

opinion that the results of the studies identified in the systematic review should be viewed with caution.

Table 14 Company summary of identified evidence

| Company summary of literature |
|---|
| The internal validity of the studies for CLAU, CLAL and KLAL is compromised in several ways. There is no accepted standard endpoint to determine success or failure of the procedure and no agreement regarding the time point at which this is measured. Consequently, the endpoints used in the studies of CLAU, CLAL and KLAL are different from case series to case series. Assessment bias may further compromise the internal validity of these studies. Rather than an objective measure of the true effects of the outcome being used, many of the key endpoints of the studies are subjective, e.g. success being defined in the opinion of the surgeon who performed the procedure following slit lamp examination only and without quantified impression cytology. Furthermore, the effects on VA are rarely and poorly documented, yet this is an important outcome for patients. |
| The external validity of the studies for CLAU, CLAL and KLAL is additionally compromised. In many cases, inclusion/exclusion criteria are not confined to moderate to severe LSCD due to physical or chemical burns therefore the ability to extrapolate the results to this specific population is limited. The surgical nature of the procedure also compromises external validity, i.e. different surgeons are likely to have different individual techniques and post-operative care regimens and therefore reproducibility of the reported outcomes in different treatment centres cannot be guaranteed. Reporting bias may further compromise the external validity of the evidence base for CLAU, CLAL and KLAL as it is unlikely that surgeons will be motivated to write up case series of failed surgical procedures (or indeed that this would have been published |

AE=adverse event; CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; KLAL=keratolimbal allograft; VA=visual acuity
Source: CS, p168 and p169

## *4.11 Results of the comparator studies*

The company states (CS, p159) that pooling of the comparator data was inappropriate due to the heterogeneity issues outlined in Table 14. For the outcome of VA, the company also reports that the methods of assessment differed between studies. The ERG agrees with the company that it is inappropriate to pool the data from any of the studies.

The company reports the outcomes (where available) for ocular stability and VA from studies of CLAU and CLAL/KLAL (CS, p158 and p159). The company's observations are listed here as bullet points.

### 4.11.1 Ocular stability

**CLAU**

- Of the 11 studies providing data on CLAU, only five studies were conducted exclusively in patients with ocular burns.[11,23,27,69,74] In the remaining six studies, the proportion of patients with ocular burns varied from 21% to 85%.[26,62,70,73,78,79] Separate results were not reported for ocular burn patients, although the Dua[62] and Miri[26] studies noted 100% of all patients achieved ocular stability.
- Success rates were available for four[23,27,76] of the five studies providing data on CLAU in patients with ocular burns. The success rates were 14/16 (87.5%) or 14/21 (66.7%) with cases requiring a second transplantation taken into account], 5/6 (83.3%), 15/16 (94%) and 6/6 (100%).[11,23,27,69] The ERG notes that all four studies were conducted in patients with unilateral LSCD.

**CLAL/KLAL**

- Of the 15 studies providing data on CLAL/KLAL, only four studies[11,27,49,67] were exclusively in patients with ocular burns. In the remaining 11 studies,[26,63,65,66,68,72,77-81] the proportion of patients with ocular burns varied from 11% to 60%. With the exception of Maruyama-Hosoi,[72] separate results were not reported for ocular burn patients.
- Only three of the studies[11,27,49] providing data on CLAL/KLAL were conducted exclusively in ocular burns patients and reported success rates. The success rates were 4/5 (80%), 20/20 (100%) and 6/10 (60%). Additionally, in the Maruyama-Hosoi[72] study, success was seen in 41% of the ocular burns patients. The ERG notes that two studies[11,49] were conducted in patients with unilateral LSCD (n=25) and two studies[27,72] were conducted in patients with bilateral LSCD.

### 4.11.2 Visual acuity

**CLAU**

- Of the 11 studies providing data on CLAU, only five studies[11,23,27,69,74] were conducted exclusively in patients with ocular burns. In the remaining six studies,[26,62,70,73,78,79] the proportion of patients with ocular burns varied from 21% to 85%. Of the 15 studies providing data on CLAL/KLAL, only four studies[11,27,49,67] were conducted exclusively in patients with ocular burns. In the remaining 11 studies, the proportion of patients with ocular burns varied from 11% to 60%.[11,27,49,67]
- In studies investigating CLAU exclusively in patients with moderate to severe LSCD due to ocular burns where VA was assessed, there was a broad range of VA outcomes reported (20% to 100% of patients with improvement).[11,23,27,69,74] In the four studies[23,27,69,74] providing VA data on CLAU, improvement was seen in 6/6 (100%), 9/13 (69%), 1/5 (20%), and 10/10 (100%) patients. The ERG notes that all four studies were conducted in patients with unilateral LSCD.

**CLAL/KLAL**

- Of the 15 studies providing data on CLAL/KLAL, only four studies[11,27,49,67] were exclusively conducted in patients with ocular burns. In the remaining 11 studies,[26,63,65,66,68,72,77-81] the proportion of patients with ocular burns varied from 11% to 60%.
- In studies investigating CLAL/KLAL exclusively in patients with moderate to severe LSCD due to ocular burns where VA was assessed, there was a broad range of outcomes reported (65%-100%).[27,49,67] In the three studies[27,49,67] providing VA data on CLAL/KLAL, improvement was seen in 13/20 (65%), 8/10 (80%) and 17/17 (100%) patients. The ERG notes that one study was conducted in patients with unilateral LSCD, one study was conducted in patients with bilateral LSCD and one study was conducted in a mixed patient group.

### 4.11.3 Adverse events

The company summarises the AE data available from the studies for CLAU and CLAL/KLAL (Table 15). The company states that AE data were not available from studies reporting treatment with BSC.

Table 15 Adverse events reported in studies of CLAU and KLAL

| Study | Adverse events |
|---|---|
| **CLAU** | |
| Dua 2000[62]<br>N=6 | No intraoperative complications, infection or graft failure were reported. Post-operatively keratitis occurred in 17% of patients and one patient developed filamentary keratitis along the edge of the donor site. |
| Ivekovic 2005[69]<br>N=6 CLAU<br>N=4 CLAU+AMT | No infection, limbal graft failure or slippage of tissue was reported. In this study, there were no intraoperative complications, refractive changes or corneal neo-vascularisation in any of the donor eyes. |
| Kenyon 1989[70]<br>N=26 | No intraoperative complications, infections or graft failure were reported. |
| Meallet, 2003[73]<br>N=5 CLAU+AMT | A transient epithelial defect in one eye and migration of pigmented epithelium onto the AMT-covered limbus in another eye was reported. |
| Tan, 1996[78]<br>N=9 | CLAU failure occurred in two patients (who had chronic contact lens-associated epitheliopathy). One contact lens wearer had epithelial dysplasia in the fellow eye at the previous donor site. Subclinical involvement of the fellow eye is suggested as a reason for graft failure and donor eye complications in these eyes. |
| **CLAL/KLAL** | |
| Eslani, 2015[63]<br>N=5 KLAL | Mean time to graft rejection 52 months. |
| Gomes, 2003[27]<br>N=10 Lr-CLAL | Reconstruction failed in three cases (75%) in the first 6 months and in one (25%) >1 year after the surgery. One of these three subjects in whom treatment failed in the first 6 months presented with graft necrosis on the eighth day after the surgery. The other two patients had severe dry eye with keratinisation.<br>Systemic AEs with the use of immunosuppression were not observed in any case. |
| Han, 2011[65]<br>N=22 KLAL | Graft failure in 42% (87% reversed). Raised intra-ocular pressure was reported in 33% of patients, epithelial defect in 42% of patients and symblepharon in 18% of patients. |
| Holland, 1996[66]<br>N=21 KLAL | 54% rejection. |
| Huang, 2011[67]<br>N=17 Lr-CLAL | Allograft rejection in 18% of eyes. |
| Ilari, 2002[68]<br>N=20 KLAL | Graft failure 46% at 1 year, 67% at 2 years and 73% at 3 years. Raised IOP was reported in 26% of patients, and corneal necrosis and microbial keratitis each in 13% of patients. |
| Maruyama-Hosoi, 2006[72]<br>N=78 KLAL | 13% rejection, 33% raised IOP, 8% infections, 4% corneal perforation and 2.5% retinal detachment. |
| Solomon, 2002[77]<br>N=31 KLAL+AMT | 10/39 eyes (25.6%) developed raised intra-ocular pressure, 14 eyes (35.9%) developed persistent epithelial defects. 3 eyes developed microbial keratitis. |
| Tan, 1996[78]<br>N=9 Lr-CLAL and CLAL-CD | A range of adverse events reported in 77.8%, including cataract, glaucoma, spastic entropion, keratitis, infection and acute rejection after stopping cyclosporine. |
| Titiyal, 2015[49]<br>N=10 Lr-CLAL<br>N=10 KLAL | There were no intraoperative complications, such as damage to muscle during symblepharon release or corneal perforation. Up to the minimum follow-up period of 6 months none of the eyes in either group developed any infection or necrosis of cornea. |
| Tsai, 1994[80]<br>N=16<br>CLAL-CD | No graft failure. |
| Tsubota, 1995[81]<br>N=9 CLAL-CD | Aphakia was reported in 56% of patients, bullous keratopathy in 67% of patients, and glaucoma and cataract each in 30% of patients. |

AE=adverse event; AMT=amniotic membrane transplantation; CLAU=conjunctival limbal autograft; CLAL=conjunctival limbal allograft; CLAL-CD=conjunctival limbal allograft from a cadaveric donor; KLAL=keratolimbal allograft; Lr-CLAL=live relative conjunctival limbal allograft

Source: CS, Table 16 and Table 17

The company sought the opinion of clinical experts[51] to ascertain the types and frequency of AEs associated with CLAU, CLAL/KLAL and BSC in clinical practice in England (CS, p163 and p164).

For CLAU, clinical advice to the company (CS, p163) is that 10% of engraftments fail and will cause persistent epithelial defect in half of the cases. Infection occurs in up to 20% of grafted eyes and in up to 5% of donor eyes. Glaucoma (secondary to the post-operative use of topical steroids) is recorded in 5-10% of patients. Between 20% and 30% of patients experience failure of their CLAU treatment (with a recurrence of LSCD) within 10 years.

For CLAL/KLAL, clinical opinion to the company (CS, p164) is that 20% of engraftments fail and will cause persistent epithelial defect in half of the failures. Infection (mainly bacterial or fungal) occurs in up to 20% of grafted eyes and in up to 5% of donor eyes for Lr-CLAL. Glaucoma (secondary to post-operative immunosuppression) is recorded in 10% of patients. All CLAL/KLAL treatments fail (with a recurrence of LSCD) within 3 to 5 years.

For BSC, clinical advice to the company is that patients are likely to experience inflammatory flare-ups and treatment failures that result in epithelial defects. Approximately 90% of patients experience one flare-up and 50% of patients experience two flare-ups annually. There are also patients who experience three flare-ups each year. Approximately 5% of patients experience microbial keratitis once each year and 10% to 20% of patients need hospital treatment for infection or persistent epithelial defect each year. Infection and persistent epithelial defect are treated in hospital for between 5 and 7 days (but length of stay can be up to 14 days). Glaucoma resulting from steroid treatment is reported in 10% of patients who are treated chronically with steroids.

### 4.11.4 Health-related quality of life

No HRQoL data are reported in any of the comparator studies.

## *4.12 Conclusions of the clinical effectiveness section*

No RCTs were identified for inclusion in this appraisal. The main evidence presented in the CS is derived from a retrospective, case series study (HLSTM01) of 104 patients with moderate to severe LSCD. The data from the HLSTM01 case series study suggest that Holoclar may be a promising treatment for this population; however the ERG notes the lack of follow-up data beyond 1 year for the majority of patients.

The company's systematic literature reviews for the clinical effectiveness of Holoclar and the clinical effectiveness of comparator technologies yielded studies that were largely retrospective and observational and included small numbers of patients. The ERG agrees with the company that whilst the HLSTM01 case series study is also retrospective and

observational, it includes substantial numbers of patients. The company has attempted to minimise several potential sources of bias, however, methodological flaws remain.

All of the patients, except one, in the HSLMT01 case series study had only one eye treated with Holoclar. The company states (CS, p12) that one of the major benefits of Holoclar is that it can be used in patients with bilateral LSCD who have at least 1-2mm$^2$ of healthy limbus in one eye. However, no clinical effectiveness evidence is presented in the CS to support the use of Holoclar to treat two eyes in a single patient.

The ERG notes that the data reported in the CS includes p-values; the authors draw statistical conclusions rather than describe summary statistics. The ERG considers that by reporting the p-values and performing hypothesis testing, the company is suggesting that treatment with Holoclar is successful in a group of patients when the purpose of the case series study was descriptive only.

The company's systematic review of comparator treatments identified one randomised study[49] of CLAL versus KLAL in 20 patients with unilateral LSCD. The remaining studies reported the use of CLAU, CLAL or KLAL in case studies, case series studies, or retrospective cohort studies. The company said it was inappropriate to pool the data from any of the identified studies due to differences in patient populations, surgical techniques and reporting of outcomes. The ERG agrees that any pooling of data from the comparator studies is inappropriate.

There are no HRQoL data available for Holoclar or for any of the comparators. This means that the HRQoL benefits of treatment with Holoclar, and whether there are more HRQoL benefits with Holoclar compared with the comparator treatments, are unknown.

# 5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of Holoclar for the treatment of moderate to severe LSCD due to ocular burns.

The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company also provided electronic versions of the economic models, which were developed in Microsoft Excel.

## *5.1 ERG comment on company review of cost effectiveness evidence*

A systematic review was conducted to summarise findings from published cost effectiveness studies that are relevant to the decision problem. Full details of the strategies used to locate cost effectiveness evidence were reported in Section 5.1 and Appendix 4 of the CS. This search included indication terms, population terms and a cost effectiveness search filter. The cost effectiveness searches were date limited from January 1989 to January 2016; the searches were carried out in January 2016. The company searched the following databases: Embase, Medline (through PubMed), Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials and Cochrane Methodology Register) and Econlit. The company reported results from grey literature searches of the following conference sites: American Academy of Ophthalmology (AAO), European Association for Vision and Eye Research (EVER), European Society of Ophthalmology (ESO), Investigative ophthalmology & visual science (IOVS), The Royal College Of Ophthalmologists (RCO) Annual Congress and World Congress of Ophthalmology (WCO).

### 5.1.1 Eligibility criteria used in study selection

Two reviewers independently applied the inclusion/exclusion criteria used to facilitate study selection.

Inclusion criteria:

- Published in English and non-English
- Human population
- Patients with a confirmed diagnosis of LSCD.

Exclusion criteria:

- Outside of scope, i.e. did not address the cost effectiveness of CLAU, CLAL, KLAL or Holoclar
- Studies that were conducted in paediatric patients (aged <18 years)
- No cost effectiveness data presented for CLAU, CLAL, KLAL or Holoclar.

The ERG is satisfied that these criteria are relevant to the decision problem.

### 5.1.2 Included and excluded studies

The company identified one relevant cost effectiveness analysis by Fordham[82] and this study is included in the economic literature review (see Table 16 for study details); the data are available from an abstract publication.

Table 16 Summary of published cost effectiveness studies

| Author, journal, year | Study location, design and duration | Intervention | Primary outcomes | Duration of follow-up | Primary outcome results |
|---|---|---|---|---|---|
| Fordham, Value in Health, 2015[82] | HLSTM01<br>UK, retrospective, case-series, non-randomised, non-controlled, multicentre clinical study | GPLSCD01 (n=99)<br>Conservative treatment (n=not given) | VA and symptoms (pain, burning and photophobia) to assess QoL and QALYs (cost effectiveness analysis) | 10 years | Patients under conservative treatment had between 10.29 and 17.24 QALYs, depending on LSCD severity, whereas patients treated with GPLSCD01 showed between 15.93 and 22.49 QALYs, with a total utility gain between 5.25 and 6.04 QALYs in the GPLSCD01 group, this result being already discounted by 3.0%, in compliance with NICE guidelines.<br>Due to the utility gain, GPLSCD01 would meet NICE conventional ICER thresholds (20,000 – 30,000 GBP/QALY) up to a treatment cost of 150,000 GBP. |

GPLSCD01=Holoclar; VA=visual acuity; QoL=quality of life; QALYs=quality adjusted life years; LSCD=limbal stem cell deficiency; NICE=National Institute for Health and Care Excellence; GBP=British pound
Source: CS, Table 19

### 5.1.3 Findings from the cost effectiveness review

In the cost effectiveness analysis by Fordham,[82] the group of patients modelled to receive a Holoclar transplant demonstrated a utility gain between 5.25 and 6.04 QALYs. Resource use and costs were not estimated but the authors considered that, due to the magnitude of benefit, Holoclar costs of up to £150,000 would be warranted.

[redacted]

[redacted]

## 5.2 ERG critique of the company's literature review

In summary, the ERG concludes that the company's searches were carried out to an adequate standard. The ERG considers that the searches accurately reflect the population described in the decision problem and, where relevant, the indication described in the final scope issued by NICE. The ERG is confident that no relevant references were missed.

The ERG has some reservations about the quality of the included study. It is difficult to decipher from the abstract and the company's critique, received via the clarification response, whether the methodology is robust. Given the methodological issues highlighted by the company, the ERG does not place any weight on the results presented in the abstract.

## 5.3 Summary and critique of the company's submitted economic evaluation by the ERG

### 5.3.1 Model structure

The company has submitted two models. One relates to patients with unilateral LSCD and the other to patients with bilateral LSCD. Each model comprises two parts:

1. decision tree capturing the acute treatment pathway
2. Markov model capturing the longer-term outcomes.

The company's description of the decision tree element of their model for patients with unilateral LSCD is provided in Box 2.

Box 2 Company's description of the decision tree component of the company's model for patients with unilateral LSCD

> Patients initially undergo a biopsy procedure, if this biopsy is successful they progress to implantation with HOLOCLAR. If the initial biopsy procedure is unsuccessful they undergo a second biopsy procedure, if this is successful they progress to HOLOCLAR implantation, if it is unsuccessful, they are classed as a failure and enter the Markov model in the Failure state. Following a successful biopsy, the patient undergoes HOLOCLAR implantation. If the implantation is successful, they enter

the Stable Month 1 to 12 state in the Markov model. If the implantation is unsuccessful they enter the Failure state. Each biopsy involves an associated cost and health related quality of life decrement.

Source: CS, p81

A schematic of the Markov component of the company's model for patients with unilateral LSCD is provided in the CS and reproduced in Figure 1.

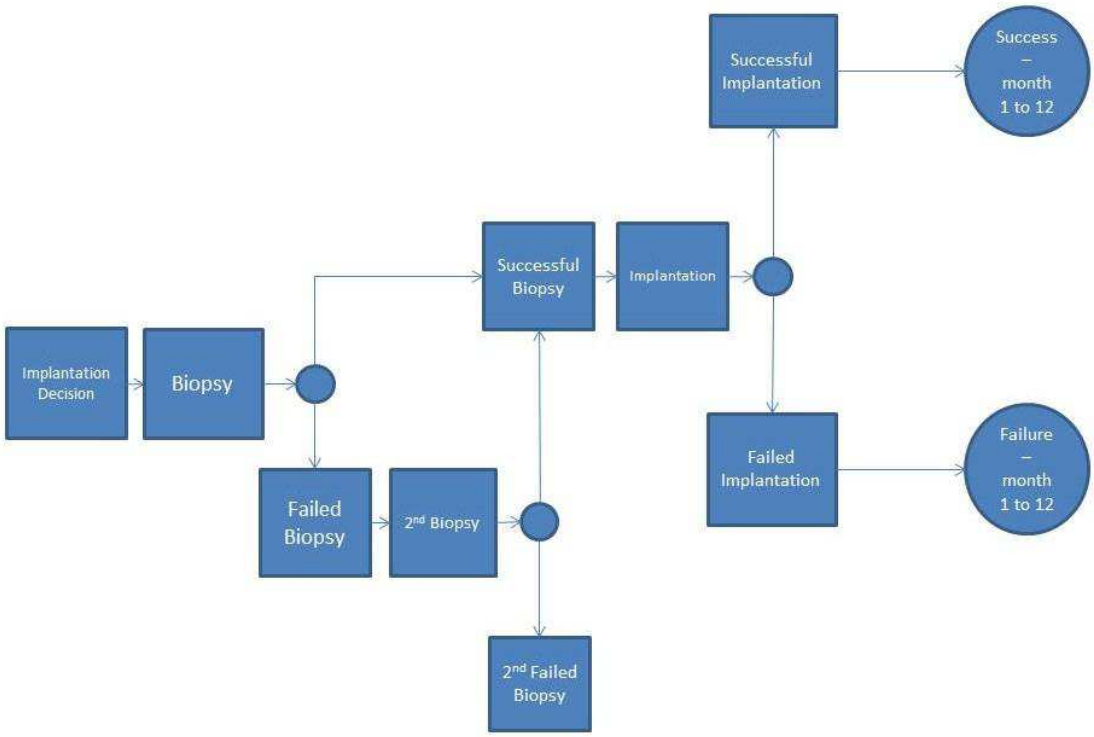


Figure 1 Schematic of the decision tree component of the company's model for patients with unilateral LSCD

Source: CS, Figure 14

A summary of the company's description of the Markov element of their model for patients with unilateral LSCD is provided in Box 3. The same model structure has been used for the intervention and the comparators except, for patients receiving CLAU, no biopsy procedure is required.

Box 3 Company's description of the pathway for patients with unilateral LSCD

If, a patient is deemed fit for an operation (see decision tree element of the model), patients enter the Markov model in either the *Stable months 1 to 12* state or the *Failure* state. Those in the *Stable months 1 to 12* state can either remain in that state or their implant may fail, in which case they move to the *Failure* state. For those who remain stable and progress to the *Stable post 12 months* state, some will be eligible for a keratoplasty at 12 months. Patients who enter the *Stable post 12 months* state will continue in this state or, at some point in the future, their HOLOCLAR implantation may fail, in which case they move to the *Failure* state. Patients in the *Failure* state will remain there for 1 year, at which point they either enter a second acute HOLOCLAR treatment pathway (captured by re-entering the decision tree) or they move to the *Best supportive care* state. Following a second

HOLOCLAR acute treatment pathway, the possible states are the same as for the initial pathway. Patients can undergo a maximum of three acute treatment pathways. Patients in all states may die.

Source: CS, p182

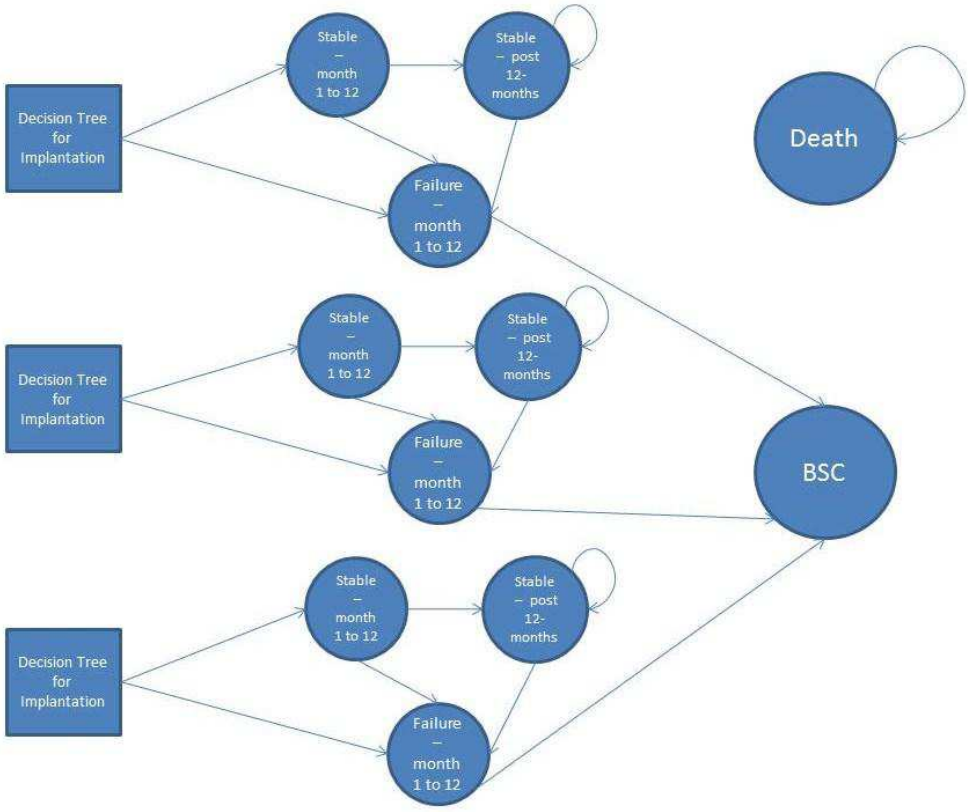


Figure 2 Schematic of the Markov component of the company's model for patients with bilateral LSCD

Source: CS, Figure 15

The model for patients with bilateral disease is the same as the model for unilateral disease with the additional complication that two eyes are being treated. It has been assumed that there would be a delay between treatments of 1 year and, therefore, for the second eye, an additional (first) year without treatment has been included.

### 5.3.2 Population

The company considers that patients participating in the HLSTM01 case series study are representative of the population described in the final scope issued by NICE, i.e. adults with moderate to severe LSCD (defined by the presence of superficial corneal neovascularisation in at least two corneal quadrants, with central corneal involvement, and severely impaired VA), unilateral or bilateral, due to physical or chemical ocular burns and a minimum of 1 to 2mm$^2$ of undamaged limbus.

The population in the model is limited to males with a mean age of 46 years and a VA score of 10.

### 5.3.3 Interventions and comparators

There is no standard treatment for patients with severe to moderate LSCD in the NHS. This appraisal considers the comparison of Holoclar, an ex vivo expanded autologous human corneal eithelial cell transplant containing stem cells, with:

- conjunctival-limbal autograft (CLAU)
- limbal epithelial stem cells allografts:
    - living-related conjunctival allograft (Lr-CLAL)
    - keratolimbal allogeneic transplantation (KLAL)
- Best supportive care (BSC).

Holoclar is implemented within the company models in line with the EMA's marketing authorisation.[13]

The models also include a keratoplasty procedure for patients 1 year after a successful Holoclar transplant. One of the secondary outcomes of the HLSTM01 case series study is the number of successful keratoplasties after the transplant; the company states that a successful transplant can provide improvements to the ocular surface that enable a keratoplasty procedure to be undertaken.

### 5.3.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS and Personal Social Services (PPS). However, it should be noted that the models do not include any PPS costs. The time horizon is set at 50 years and, in the base case, both costs and outcomes are discounted at a rate of 1.5%. The company explains that a rate of 1.5% has been used as the technology has a prolonged effect and can return patients to a high utility state.

### 5.3.5 Treatment effectiveness and extrapolation

The company states a successful transplant restores a stable cornea with little or no defects or blood vessels in the cornea. Stromal scarring is the second key clinical parameter. The probability of a successful transplant with each of the comparator interventions is sourced from the literature (pooled data), while the evidence for Holoclar comes from analysis of the HLSTM01 case series study data.

There is no direct evidence of the HRQoL associated with a cornea in good condition with or without stromal scarring. The company has therefore conducted regression modelling to estimate the relationship between the appearance of the cornea and stromal scarring with (i) VA and (ii) pain, burning and photophobia.

**The relationship between transplant success, stromal scarring and visual acuity**

The company examined a number of different modelling specifications and chose a random effects ordered logistic regression model to estimate the relationship between VA, transplant success and stromal scarring. The dependent variable is generated by converting VA onto a 13-point scale from Light Perception (LP) to 10/10 Best Corrected Visual Acuity (BCVA). The model chosen by the company assumes that the relationship between VA and transplant success is the same as that observed in the HLSTM01 case series study at 12 months and that this relationship remains constant over time.

The company models assume that the relationship between a successful transplant and VA, generated from an analysis of Holoclar data, is the same regardless of the treatment.

On the basis of an eye-level random effects parameter that demonstrates a large variation in underlying VA, the company models three different baseline levels of VA: average, good and poor. Good is defined as being in the top 25% of the estimated random effects and poor in the bottom 25% and then relevant proportioned distribution mean values are given to these groups. The intercept values for poor/average/good underlying VA are -2.3/0/2.3 respectively.

The CS (Tables 23 to 25) shows the probability of each VA level, calculated from the regression coefficients, for six distinct groups: patients with and without stromal scarring at baseline, people in whom the transplant fails (with and without stromal scarring) and people whose transplant is a success (with and without stromal scarring).

**The relationship between pain/burning/photophobia and successful transplantation and stromal scarring**

Pain, burning and photophobia are identified as symptoms that have a negative impact on HRQoL. Patients in the HLSTM01 case series study self-reported the presence and severity of each of these symptoms by choosing from one of four categories (i.e., none/mild/moderate/severe) at each examination.

The company combines the data from all observations of the pain/burning/photophobia symptoms by taking the highest result overall for each patient and creating an ‘any’ category for use as the dependent variable in the regression analysis.

In the regression model, the eye-level random effects parameter used by the company demonstrated less heterogeneity for pain/burning/photophobia than for VA; the company therefore models pain/burning/photophobia for the average patient only. The probability of reporting symptoms at different levels of severity at baseline and following transplant success or failure, and depending on the presence of stromal scarring, is shown in Table 17.

Table 17 Predicted probabilities of pain/burning/photophobia

| | Baseline with SS | | Baseline w/o SS | | Transplant failure with SS | | Transplant failure w/o SS | | Transplant success with SS | | Transplant success w/o SS | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XB | 2.7899 | | 1.7497 | | 1.8479 | | 0.8077 | | 1.0402 | | 0 | |
| Pain/burning/photophobia | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** | **Cum Prob** | **Prob** |
| None | 57.47% | 57.47% | 79.27% | 79.27% | 77.61% | 77.61% | 90.75% | 90.75% | 88.60% | 88.60% | 95.65% | 95.65% |
| Mild | 85.95% | 28.47% | 94.54% | 15.27% | 94.01% | 16.40% | 97.80% | 7.05% | 97.24% | 8.63% | 99.01% | 3.35% |
| Moderate | 99.44% | 13.49% | 99.80% | 5.26% | 99.78% | 5.77% | 99.92% | 2.13% | 99.90% | 2.67% | 99.97% | 0.96% |
| Severe | 100.00% | 0.56% | 100.00% | 0.20% | 100.00 % | 0.22% | 100.00% | 0.08% | 100.00% | 0.10% | 100.00% | 0.03% |

SS=stromal scarring; XB=linear prediction of fitted model; Cum=cumulative; Prob=probability
Source: CS, Table 30

**The relationship between transplant success, keratoplasties and stromal scarring**

The probability of stromal scarring from the HLSTM01 dataset is used to indirectly estimate the impact that keratoplasty has on VA. The probability of stromal scarring at different points in the pathway is estimated from the outputs of a random effects logistic regression and shown in Table 18.

Table 18 Predicted probabilities of stromal scarring

| | Baseline | Failed transplant | Successful transplant | Successful transplant plus successful keratoplasty |
|---|---|---|---|---|
| XB | -2.2404 | -2.08286 | -2.0441 | 1.4884 |
| No stromal scarring | 9.62% | 11.08% | 11.46% | 81.58% |
| Stromal scarring | 90.38% | 88.92% | 88.54% | 18.42% |

XB=linear prediction of fitted model
Source: CS, Table 34

**Relationship between underling eye heterogeneity and length of follow-up**

The company performed regression analysis to test whether the dataset from HLSTM01 was biased and checked whether longer follow-up occurred in patients with healthier or more favourable eyes; the company concludes that this is not the case.

### 5.3.6 Health-related quality of life

The relationship between utility and level of VA, in one eye or both eyes is unclear. A systematic literature review undertaken by the company revealed no studies reporting utility scores relating to LSCD. Findings did, however, suggest that utility or utility decrements may be driven by:

- loss of VA
- pain/burning/photophobia
- a cosmetic disfigurement.

The company has undertaken two broad approaches to identify utility values to use in the models, namely:

1. a bespoke standard gamble (SG) stated preference exercise (520 members of the public)
2. the burden of disease systematic review undertaken by the company identified key symptoms that drive the overall utility of patients with LSCD (VA), pain, burning, photophobia and disfigurement). A search of broader literature was conducted to identify disutility values associated with these utility drivers.

Pain is a probabilistic function of health states, disfigurement is assumed to be present in all states except for those patients who are in a stable condition and do not have stromal scarring.

A summary of the utility values used in the company's base case analysis is displayed in Table 19.

Table 19 Summary of utilities associated with the different Markov model health states

| State | VA based utility | Pain/burning/ photophobia | Disfigurement | Overall utility |
|---|---|---|---|---|
| Baseline with stromal scarring | 0.56 | -0.019 | -0.318 | 0.223 |
| Baseline without stromal scarring | 0.60 | -0.007 | -0.318 | 0.275 |
| Transplant failure/ BSC with stromal scarring | 0.57 | -0.008 | -0.318 | 0.244 |
| Transplant failure/ BSC without stromal scarring | 0.63 | -0.003 | -0.318 | 0.309 |
| Transplant success – stable with stromal scarring | 0.60 | -0.004 | -0.318 | 0.278 |
| Transplant success – stable without stromal scarring | 0.67 | -0.001 | - | 0.669 |
| Death | 0 | - | - | 0 |

BSC=best supportive care; VA=visual acuity
Source: CS, Table 48

**Adverse events**

The company identified that reports of AEs from observational studies (CS, Section 4.12) are inconsistent and incomplete thus deriving absolute and relative risk values was not possible. The company, therefore, sought advice from clinical experts.[51] The glaucoma rates used in the company models are displayed in Table 20.

Table 20 Glaucoma rates used in the company models

| Procedure | Rate | Source |
|---|---|---|
| CLAU | 5% | Expert opinion[51] |
| Lr-CLAL | 10% | Expert opinion[51] |
| KLAL | 10% | Expert opinion[51] |
| Holoclar | 3.5% | SmPC[30] |

CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; SmPC=summary of product characteristics
Source: Submitted economic models

### 5.3.7 Resources and costs

The company presents the procedural resource use and costs in two sections: those relating to the initial biopsy (Table 21) and those associated with the main transplant (Table 22). The ERG identified some minor discrepancies between the values used in the CS and the values used within the models.

## Extraction biopsy

Table 21 Resource use and costs for cell extraction biopsy

| Resource item | Cost | Treatment | Number | Source |
|---|---|---|---|---|
| Minor eye procedure | £675.73 | Holoclar | 1 | NHS Reference Cost: Minor, Cornea or Sclera Procedure for Extraction[83] |
| | | CLAU | 0 | |
| | | Lr-CLAL | 1 | |
| | | KLAL | 0 | |
| Amniotic membrane | £[redacted] | Holoclar | 0 | Frozen amniotic membrane 2x2cm NHS Blood and Transport |
| | | CLAU | 1 | |
| | | Lr-CLAL | 1 | |
| | | KLAL | 2 | |
| Bandage contact lens applied by an ophthalmologist | £4.17 | CLAU only | 1 | http://www.visiondirect.co.uk/purevision |
| Outpatient appointment | £60.13 | Holoclar | 1 | NHS Reference Cost: Average cost of a medical ophthalmology outpatient appointment[83] |
| | | CLAU | 0 | |
| | | Lr-CLAL | 5 | |
| | | KLAL | 0 | |
| Antibiotic eye drops | £0.007 | All | 4 x day, 3 weeks | MIMs Online[84] Chloramphenicol 0.5% 10ml £1.45 |
| Steroid eye drops | £0.01 | All | 4 x day, 3 weeks | MIMs Online[84] Prednisolone sodium phosphate 0.5% 10ml £2- 100 |
| Artificial tears | £0.037 | All | 4 x day, 3 weeks | MIMs Online[84] Carmellose Sodium 0.5% 10mL |

CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft
Source: Submitted economic models

## Main transplant

Table 22 Resource use and costs for cell implantation

| Resource item | Cost | Treatment | Number | Source |
|---|---|---|---|---|
| Holoclar | £[redacted] | Intervention-specific costs | 1 | CS |
| CLAU | £0 | | 1 | |
| Ir-CLAL | £0 | | 1 | |
| KLAL | £[redacted] | | 1 | Single Cornea- NHS Blood and Transplant |
| Surgery | £2,934.30 | All | | NHS Reference Cost: Very Complex, Cornea or Sclera Procedures with CC Score 0-1[83] |
| Amniotic membrane | £[redacted] | Holoclar | 0 | Frozen amniotic membrane 2x2cm NHS Blood and Transport |
| | | CLAU | 1 | |
| | | Lr-CLAL | 1 | |
| | | KLAL | 2 | |

CS=company submission; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft
Source: Submitted economic models

## Health state resource use and costs

The resource use assumed for post-transplant health states in the models are described in Table 23.

Table 23 Resource use and costs in modelled health states

| Resource item | Cost | Treatment | Number | Source |
|---|---|---|---|---|
| **Stable first 12 months** | | | | |
| Antibiotic eye drops | £0.007 | Holoclar | 0 | MIMs Online[84] Chloramphenicol 0.5% 10ml £1.45 |
| | | CLAU, Lr-CLAL, KLAL | 4 x day, first 3 months | |
| Steroid eye drops | £0.01 | Holoclar | 0 | MIMs Online[84] Prednisolone sodium phosphate 0.5% 10ml £2 - 100 drops |
| | | CLAU, Lr-CLAL, KLAL | 4 x day, first 3 months | |
| Artificial tears | £0.037 | Holoclar | 0 | MIMs Online[84] Carmellose Sodium 0.5% 10mL |
| | | CLAU/Lr-CLAL, KLAL | 4 x day, first 3 months | |
| Autologous serum eye drops | £[redacted] | Holoclar | 0 | NHS Blood and Transplant |
| | | CLAU/Lr-CLAL, KLAL | 2 | |
| Outpatient appointments* | £60.13 | Holoclar | 5 | NHS Reference Cost: Average cost of a medical ophthalmology OP appointment[83] |
| | | CLAU/Lr-CLAL, KLAL | 10 | |
| Immunosuppressants** | | For 12 months for patients who received Lr-CLAL or KLAL | | |
| **Stable post-12-months:** No on-going treatment required | | | | |
| **Failure**: No cost associated with failure*** | | | | |
| **Best supportive care** | | | | |
| Regular ophthalmology outpatient appointments | £60.13 | All | 6 per year | NHS Reference Cost: Average cost of a medical OP ophthalmology appointment[83] |
| Antibiotic eye drops | £0.007 | All | 4 x day | MIMs Online[84] Prednisolone sodium phosphate 0.5% 10ml £2- 100 drops |
| Steroid eye drops | £0.01 | All | 4 x day | MIMs Online[84] Chloramphenicol 0.5% 10ml £1.45 |
| Artificial tears | £0.037 | All | 4 x day | MIMs Online[84] Carmellose Sodium 0.5% 10mL |
| Flare-ups | | Treated with autologous serum eye drops and a course of oral antibiotics | 2 x year | |
| Autologous eye drops | £[redacted] | | | NHS Blood and Transplant |
| Oral antibiotics | £0.09 | | | MIMs Online[84] - Oral Tetracycline 28 packet £2.62 |
| **Keratoplasty** | | | | |
| Keratoplasty product | £[redacted] | All | | Single Cornea- NHS Blood and Transplant |
| Major eye procedure | £2,934.30 | All | | NHS Reference Cost: Very Complex, Cornea or Sclera Procedures with CC Score 0-1[83] |
| Outpatient appointments | £60.13 | All | 6 | NHS Reference Cost: Average cost of a medical ophthalmology OP appointment[83] |
| Antibiotic eye drops | £0.007 | All | 4 x day, 2 months | MIMs Online[84] Prednisolone sodium phosphate 0.5% 10ml £2- 100 drops |
| Steroid eye drops | £0.01 | All | 4 x day, 2 months | MIMs Online[84] Chloramphenicol 0.5% 10ml £1.45 |
| Artificial tears | £0.037 | All | 4 x day, 2 months | MIMs Online[84] Carmellose Sodium 0.5% 10mL |

CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; OP=outpatient
Source: CS, Section 5.5 and company models
*The CS states, weekly for first 2 months, fortnightly from 3– 6 months and then monthly up to 12 months (i.e. 22 appointments)
** The costs of immunosuppressants are not included within the models
***The first 12 months post-transplant failure is allocated the same resource use as BSC

**Adverse event costs**

The cost in the models associated with treating glaucoma is £1,151 taken from the ERG report for aflibercept for treating diabetic macular oedema.[85]

### 5.3.8 Cost effectiveness results

Total and incremental costs and QALYs for the comparison of Holoclar with the available treatment options for unilateral and bilateral LSCD are shown in Table 24 to Table 27. In the base case, for both unilateral and bilateral disease, all treatment options are dominated by CLAU; CLAU is the most effective and cheapest treatment option of all treatments considered. When CLAU is removed from the decision-space and Holoclar is compared to the most effective alternative treatment (KLAL, in both populations), Holoclar generates additional benefits at an additional cost.

A breakdown of the proportions of patients in each health state over time, the contribution of each of the components to the total utility of each intervention and the share of total costs attributable to each treatment or BSC are shown in Tables 53 to 57 in the CS.

For clarity, the ERG also presents a pair-wise comparison of Holoclar with each of the comparator options. The results for unilateral disease are presented in

Table 25, for unilateral disease and for bilateral disease in Table 27.

Table 24 Base case results - unilateral LSCD

| | Costs | QALYs | ICER per QALY gained: each treatment versus baseline |
|---|---|---|---|
| CLAU | £22,158 | 12.64 | CLAU dominates all treatments as it is cheaper and more effective |
| Lr-CLAL | £77,434 | 9.73 | |
| KLAL | £89,256 | 9.80 | |
| Holoclar | £[redacted] | 12.09 | |
| BSC | £101,535 | 7.18 | |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: CS, Table 51

Table 25 Base case results - unilateral LSCD (pair-wise comparisons with Holoclar)

| | Incremental costs | Incremental QALYs | ICER per QALY gained: Holoclar vs comparator |
|---|---|---|---|
| Holoclar | - | - | - |
| CLAU | -£72,264 | 0.55 | Holoclar is dominated by CLAU; Holoclar is more expensive and less effective |
| Lr-CLAL | -£16,988 | -2.36 | £7,185 |
| KLAL | - £5,167 | -2.29 | £2,255 |
| BSC | £7,112 | -4.91 | Holoclar dominates BSC: Holoclar is cheaper and more effective |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: Adapted from CS, Table 51

Table 26 Base case results - bilateral LSCD

| | Costs | QALYs | ICER per QALY gained: treatment versus baseline |
|---|---|---|---|
| CLAU | £47,402 | 10.08 | CLAU dominates all treatments as it is cheaper and more effective |
| Lr-CLAL | £155,430 | 6.36 | |
| KLAL | £173,844 | 6.56 | |
| HOLOCLAR | £[redacted] | 9.25 | |
| BSC | £193,323 | 2.44 | |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: CS, Table 52

Table 27 Base case results - bilateral LSCD (pair-wise comparisons with Holoclar)

| | Incremental costs | Incremental QALYs | ICER per QALY gained: Holoclar versus comparator |
|---|---|---|---|
| Holoclar | - | - | - |
| CLAU | -£144,014 | 0.83 | Holoclar is dominated by CLAU; Holoclar is more expensive and less effective |
| Lr-CLAL | -£35,986 | -2.89 | £12,438 |
| KLAL | - £17,572 | -2.69 | £6,533 |
| BSC | £1,906 | -6.81 | Holoclar dominates BSC; Holoclar is cheaper and more effective |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: Adapted from CS, Table 52

### 5.3.9 Sensitivity analyses

**Deterministic sensitivity analysis**

The company presents a number of scenario analyses based on changes to some key assumptions in the models. The parameters varied include the discount rate, the utility value for disfigurement, the success of comparative surgical interventions and the timeframe over

which cost effectiveness is assessed in the models. The ICERs for each scenario are presented in Table 28 for unilateral disease and in

Table 29 for bilateral disease.

Table 28 Sensitivity analysis - unilateral LSCD (pair-wise comparisons with Holoclar)

| | ICER per QALY gained | | | |
|---|---|---|---|---|
| **Scenario** | **CLAU** | **Lr-CLAL** | **KLAL** | **BSC** |
| Base case | Holoclar is dominated | £7,185 | £2,255 | Holoclar dominates |
| 3.5% discount rates | Holoclar is dominated | £21,182 | £15,245 | £3,563 |
| No disfigurement utility decrement | Holoclar is dominated | £35,076 | £11,546 | Holoclar dominates |
| 3.5% discount rates, no disfigurement disutility decrement & 4 flares per year in BSC | Holoclar is dominated | £25,164 | £7,586 | Holoclar dominates |
| No disfigurement decrement, CLAU=Burcu[11] rates, Lr-CLAL=Gomes[27] rates and KLAL=Solomon[77] rates | £488,615 | £487 | £9,138 | Holoclar dominates |
| *CLAU=Burcu[11] rates, Lr-CLAL=Gomes[27] rates and KLAL=Solomon[77] rates and 22 year time horizon | £167,201 | £13,651 | £29,488 | £5,743 |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: Submitted economic models
*Costs in the model are slightly different to the costs reported in the submission

Table 29 Sensitivity analysis - bilateral LSCD (pair-wise comparisons with Holoclar)

| | ICER per QALY gained | | | |
|---|---|---|---|---|
| **Scenario** | **CLAU** | **Lr-CLAL** | **KLAL** | **BSC** |
| Base case | Dominates | £12,438 | £6,533 | Dominated |
| 3.5% discount rates | Dominates | £34,817 | £29,818 | £6,708 |
| No disfigurement utility decrement | Dominates | £31,850 | £21,861 | Dominated |
| 3.5% discount rates, no disfigurement disutility decrement & 4 flares a year in BSC | Dominates | £26,384 | £39,595 | Dominated |
| No disfigurement decrement, CLAU=Burcu[11] rates, Lr-CLAL=Gomes[27] rates and KLAL=Solomon[77] rates | £486,145 | £1,928 | £19,049 | Dominated |
| CLAU=Burcu[11] rates, Lr-CLAL=Gomes[27] rates and KLAL=Solomon[77] rates and 28 year time horizon | £255,563 | £11,368 | £27,898 | £5,060 |

QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; CLAU=conjunctival limbal autograft; Lr-CLAL=conjunctival limbal allograft from a living related donor; KLAL=keratolimbal allograft; BSC=best supportive care
Source: Submitted economic models

## Probabilistic sensitivity analysis

The company states (CS, p232) that the PSA generates cost effectiveness acceptability curves that suggest there is a 100% likelihood of CLAU being the most cost effective option.

### 5.3.10 Model validation and face validity check

The company reports that their estimates of distributions of VA states, presence of stromal scarring and pain/burning/photophobia were validated against the HLSTM01 dataset.

The company states that external validation of the costs and HRQoL of people with LSCD is not possible due to a paucity of evidence. The company highlights that (i) mapping from best seeing eye to utility is well established and (ii) utility decrements due to pain are based on established EQ-5D tariffs.

The company states the authors of the SG study conducted by the York Health Economics Consortium (YHEC) for the company (CS, Appendix 7) estimate a large utility decrement for disfigurement, which is consistent with the opinion of clinical experts.

### 5.3.11 NICE reference case checklist

Table 30 NICE Reference case checklist completed by ERG

| Attribute | Reference case | Does the de novo economic evaluation match the reference case? |
|---|---|---|
| Decision problem | The scope developed by NICE | Yes |
| Comparator(s) | As listed in the scope developed by NICE | Yes. Both unilateral and bilateral are compared with conjunctival limbal autograft (CLAU), limbal epithelial stem cells allografts (Lr-CLAL and KLAL) and BSC |
| Perspective costs | All direct health effects, whether for patients or, when relevant, carers | Yes |
| Perspective benefits | NHS and PSS | Partial - patient related direct health effects are considered. No impact on carers has been considered in the models |
| Form of economic evaluation | Cost utility analysis with fully incremental analysis | Yes |
| Time horizon | Long enough to reflect all important differences in costs or outcomes between the technologies being compared | Yes |
| Synthesis of evidence on outcomes | Based on systematic review | No. Only case series data are available for Holoclar. The company carried out a systematic review of evidence for comparator interventions. The company pooled outcome data from the review and used the pooled estimates in the submitted models. The ERG notes that heterogeneity in populations and study designs add considerable uncertainty to these pooled estimates |
| Outcome measure | Health effects should be expressed in QALYs. | Yes |
| Health states for QALY | Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults | Yes, indirectly. Utility values were mapped using data from VA studies to EQ-5D values. Symptomatic decrements to quality of life were sourced from the literature |
| Benefit valuation | Reported directly by patients and/or carers | No |
| Source of preference data for valuation of changes in HRQoL | Representative sample of the UK population | Indirectly |
| Discount rate | The same annual rate for both costs and health effects (currently 3.5%) | No. A discount rate of 1.5% for costs and benefits was used in base case. The company states that if a transplant with Holoclar is successful, then long-term benefits are achieved and patients experience high levels of utility. The ERG does not consider use of this discount rate to be valid |
| Equity | An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit | Yes |
| Sensitivity analysis | Probabilistic sensitivity analysis | The models are not fully probabilistic. Deterministic scenario analyses are presented |

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; VA=visual acuity; BSC=best supportive care

### 5.3.12 Drummond checklist

Table 31 Critical appraisal checklist for the economic analysis completed by the ERG

| Question | Critical appraisal | ERG comment |
|---|---|---|
| Was a well-defined question posed in answerable form? | Yes | |
| Was a comprehensive description of the competing alternatives given? | Yes | |
| Was the effectiveness of the programme or services established? | Yes | The data are derived from a retrospective, case series study (HLMST01) |
| Were all the important and relevant costs and consequences for each alternative identified? | Yes | Some of the assumptions in the model were unsupported by data |
| Were costs and consequences measured accurately in appropriate physical units? | Yes | |
| Were the cost and consequences valued credibly? | Yes | |
| Were costs and consequences adjusted for differential timing? | Yes | |
| Was an incremental analysis of costs and consequences of alternatives performed? | Yes | |
| Was allowance made for uncertainty in the estimates of costs and consequences? | Partial | The results of PSA are reported but many parameters lack estimates of their uncertainty, therefore the model is not fully probabilistic. Deterministic sensitivity analysis results are reported |
| Did the presentation and discussion of study results include all issues of concern to users? | Yes | |

PSA=probabilistic sensitivity analysis; ERG=Evidence Review Group

## *5.4 Detailed critique of the company's economic model*

Section 5.5.1 provides the ERG's assessment of the model structure and also the effectiveness data incorporated into the company's economic model. Sections 5.4.2 to 5.4.5 describe four issues that have a major impact on the cost effectiveness results generated by the company model (i.e., HRQoL, the discount rate, the use of autologous serum eye drops and use of KLAL on failure with Lr-CLAL).

### 5.4.1 Summary of model structure and included data

The company provided the model in MS Excel. The ERG considers that the model was reasonably well constructed with no flaws in the algorithms used to generate base case results and was straightforward to use. Some of the scenario options built into the model did not seem to function but these did not impact on the ability of the ERG to generate cost effectiveness results.

Following clinical advice, the ERG agrees with the company that CLAU is not a plausible procedure for patients with bilateral LSCD and so should not be included as a comparator.

The ERG notes the numerous data quality issues related to study design discussed in Section 4 and considers that all of the included studies in the systematic review are equally flawed. However, in contrast to the company's statement that it was inappropriate to pool the data from the comparator studies due to parameter heterogeneity, pooled estimates of the effectiveness data are used in the base case economic models. It is not clear whether this is a pooling of data from specific studies of patients with ocular burns, or is a pooling of data from all studies and all patients. However, as the individual studies have very small sample sizes, the ERG considers it doubtful that selection of any one study will produce more robust results than the pooled analysis. However, the weak evidence base from which the comparator effectiveness is drawn needs to be taken into account when assessing the robustness of the ICERs generated by the company models.

Clinical advice to the company is that Lr-CLAL and KLAL procedures all fail by 5 years. However, the company models suggest that 32.2% of patients with Lr-CLAL and 24.2% of patients with KLAL have a stable first transplant at 5 years. Whilst this could mean that the success rates of Lr-CLAL and KLAL are overstated in the company models, this assumption is consistent with the published studies[11,26,27,49,51,65,66,68,72,77-81] identified in the CS, if not with clinical opinion.

Similarly, clinical advice to the company is that 30% of CLAU transplants fail by 10 years. However, the models assume that the 86.8% of patients that have successful transplants at 12 months are considered to have successful transplants for life. The same assumption is made for Holoclar patients who have stable transplants at 12 months. The models cannot be changed to allow failure rates at 10 years without completely restructuring them and this modification is beyond the remit of the ERG. In any case, the evidence to support the restructure would only be from a single clinical opinion on CLAU and there is no evidence on 10-year survival for Holoclar beyond one patient from the HLMST01 case series study. The ERG considers it an inherent weakness in the models that longer term (post-12 months) failure rates cannot be explored. If transplant failure occurs post 12 months for CLAU and Holoclar, then the ICERs per QALY gained for both treatments compared to the alternative procedures would increase. The impact on the ICER per QALY gained between Holoclar and CLAU of failure post 12 months would be dependent on the relative failure rate between the two procedures, which is unknown.

The ERG requested patient level data from the HLMST01 case series study that was used to generate the clinical effectiveness results for Holoclar. The ERG considers that a simpler analysis of the data could have been performed than was carried out by the company. The company could have looked at the success rate associated with removing disfigurement and the average line increase in VA – especially given that improvement in VA was arbitrarily

grouped into the worst 25%, middle 50% and best 25% of eyes in any case. The ERG did not reproduce the logistic regressions the company undertook to generate effectiveness results. However, by checking baseline VA, stromal scarring and simple effectiveness rates, the ERG is confident that the results generated from the company's regressions and analysis of the HLMST01 dataset, and incorporated into the models, are satisfactory.

There are significant issues relating to the absence of clinical effectiveness data to support the use of Holoclar to treat both eyes in patients with bilateral LSCD and these are discussed in detail in Section 3. Due to this absence of supporting evidence, the ERG considers that, whilst the ERG modifications described in the rest of this section for bilateral model results are presented, they should be interpreted as the results of a 'what if' scenario rather than the results of a robust analysis.

### 5.4.2 Health-related quality of life

Whilst the company has made a laudable attempt to estimate utility values in a patient population for which no utility values are available, the ERG considers that the utility values associated with the different health states employed in the base case models are implausibly low. In the company's unilateral model, the health state of transplant success and keratoplasty for patients with pre-operation 'good' eyesight in the worst seeing eye has the highest utility value of 0.706 (0.692 in the bilateral model). All other states with transplant failure or BSC have a utility value below 0.360 (e.g., the utility value is as low as 0.04 for patients with poor vision and stromal scarring in the bilateral model).

For perspective, a utility value of 0.360 is lower than the utility value reported for patients with various cancers receiving palliative treatment only in the last 3 months of life.[86] These utility values are all also significantly lower than the utility values employed in other modelling work undertaken by NICE in eye-related diseases. For example, in the chronic open angle glaucoma guideline,[87] the utility values used in the model were all above 0.819 except for severe visual impairment where a base case value of 0.503 was used; in this model, the lower limit for severe visual impairment was 0.331 and this is the only value that is at all commensurate with the lower values employed in the company model. Whilst it is reported in the CS (p67) that patients may have multiple co-morbidities related to the incident resulting in LSCD that could reduce a person's HRQoL to the utility levels employed in the model, the CS and model are only concerned with utility values associated with the eye and treatment of LSCD. In the absence of utility values directly for this population, the assumption has to be made (which the company has rightly done) that the utility values reflect otherwise healthy patients only with utility decrements related to the LSCD.

The ERG considers that more appropriate utility values should be chosen to produce more realistic ICERs accepting that there is no utility set specifically for the population being modelled. There are two factors that drive the company's low utility values and, for each of these factors, alternative values can be used.

The first is the choice of VA utility values used in the company model. Using the Czoski-Murray (2009)[88] approach (Time Trade Off methodology and patients with wet age-related macular degeneration) coupled with an adjustment based on data from Finger[89] yields a maximum utility value of 0.706 assuming vision of 0.6 to 1.0 in both eyes and this utility value is used in the unilateral base case model. This value is lower than the utility value of 0.856, assuming perfect vision in both eyes, that is estimated when using the Czoski-Murray approach as described in the aflibercept STA[90] and is lower than the UK population norm of 0.840 for full health in a male patient aged 46[91] - the representative patient in the company model.

The reason for the difference in utility values from the Czoski-Murray approach[88] in the CS and the aflibercept STA[90] is not easy to determine from the information provided by the company. Whatever the underlying cause, the ERG considers that the utility values used in the model must be reflective of reality. As the maximum and minimum utilities generated by the company's approach are implausible, both compared to the population norm and to the values used in other eye disease modelling for previous submissions, an alternative method that produces higher VA utilities is preferable.

As there are no EQ-5D utility values available for VA in patients with moderate to severe LSCD due to ocular burns, the ERG carried out a non-systematic search for other potential VA utility values focussing on previous NICE guidelines and STAs in eye disease. The results of the search revealed that there are no better alternatives than those considered by the company. The ERG then considered all of the utility value options available in both the unilateral and bilateral models on the basis of the plausibility of the upper and lower values of the health states described in the company model (Table 32).

Table 32 Utility values generated by the company model for highest and lowest utility health states using different VA utility sources

| | VA utility source | | | |
|---|---|---|---|---|
| | Czoski-Murray group means (2009)[88] (Base case) | Brown (2003)[92] | Brown (2008)[93] | Czoski-Murray OLS model (2009)[88] |
| Highest utility value health state in economic models (unilateral, good prior vision and successful transplant and keratoplasty) | 0.706 | 0.861 | 0.920 | 0.799 |
| Lowest utility value in economic models (bilateral, poor prior vision and unsuccessful transplant with stromal scarring) | 0.04 | 0.285 | 0.07 | -0.208 |

OLS=Ordinary Least Squares; VA=visual acuity
Source: adapted from CS, Table 43 and company model

The values in Table 32 are the results generated by the company model. As shown in Table 32, the lower bound utility values are implausible for all but those generated from the Brown 2003 values.[92] Even though the lower bound is lower than values reported in other eye disease related STAs and guidelines, such as the chronic open angle glaucoma guideline,[87] the upper bound is in line with the 0.840 UK population norm for the reference patient entering the model. Arguments can be made for and against the methodology used in any of the studies considered in Table 32 but the ERG considers that plausibility of results has to be the deciding factor and the most plausible values are generated from Brown 2003.[92]

Using the Brown 2003[92] utility values decreases the QALY gain from Holoclar in the unilateral case from 2.36 to 2.24 versus Lr-CLAL with the ICER increasing to £7,576 per QALY gained. Versus KLAL, QALY gain is reduced from 2.29 to 2.18 with the ICER increasing to £2,367 per QALY gained. Versus BSC, QALY gain is reduced from 4.91 to 4.33, with Holoclar still dominating BSC. Holoclar remains dominated by CLAU although the QALY gain with CLAU decreased from 0.55 to 0.52.

In the bilateral case, QALYs decreased from 2.89 to 2.59 versus Lr-CLAL with the ICER increasing to £13,916 per QALY gained. Versus KLAL, QALY gain is reduced from 2.69 to 2.34 with the ICER increasing to £7,512 per QALY gained. Versus BSC, QALY gain is reduced from 6.81 to 5.33, with Holoclar still dominating BSC. There is no comparison of Holoclar versus CLAU.

The second reason for the low utility values is the 0.318 decrement applied for disfigurement in any eye to all patients that do not have a successful keratoplasty. The decrement is applied equally regardless of the extent of disfigurement and is derived from the SG study conducted by the York Health Economics Consortium (YHEC) for the company (CS, Appendix 7).

Compared to KLAL and Lr-CLAL, the ERG calculated that 80% of the QALY gain generated in the company unilateral model base case from Holoclar arises from the removal of disfigurement, so not only is it important to obtain a robust value for disfigurement to generate plausible overall utility values, it is also important as it is the biggest driver of QALY gains in the company's model.

The company is rightly cautious about using the results of the SG study and notes several contradictory values that suggest that the individuals who participated in the study did not fully understand the questions being asked. However, the company uses a utility value for disfigurement in their base case unilateral and bilateral models that is drawn from a regression analysis of the findings from this same SG study. The company's regression analysis does not (and cannot) rectify the underlying data quality issues in the SG study and so the value used in the company model is no more robust than any of the values drawn directly from the SG study.

The company has also assumed that the disfigurement utility is the same regardless of a patient's level of corneal opacity, corneal neovascularisation and inflammation. The ERG notes there was a distribution of these parameters in the baseline population of the HMST01 case series study. The ERG considers that it is likely that patients therefore have a range of severity of disfigurement. Essentially the same disutility is applied in the company models whether a patient has just one affected eye with inflammation or both eyes have severe corneal opacity, corneal neovascularisation and inflammation. Application of just one disutility value for disfigurement – especially one so high – does not therefore accurately measure the impact of disfigurement in this population.

The ERG conducted a non-systematic review of the literature and found no utility values for eye disfigurement other than that for cataracts from the aflibercept STA.[90,94] For comparison, the decrement of 0.318 is greater than that reported by the authors of a review of utility values for economic modelling in Type 2 diabetes for amputation of a limb (0.280) or for cataracts (0.140) as reported in the aflibercept ERG report.[90] Disfigurement is a HRQoL issue for patients with LSCD. However, as there are no robust utility values available, the actual impact on utility remains unknown but the ERG's comparison to other utility values such as amputation and cataracts suggests that the decrement applied by the company may be too high.

The ERG considers that, whilst not directly comparable to eye damage from LSCD, cataracts produce opaqueness in the eye, albeit in the lens rather than in the cornea, so utility values associated with cataracts may be a reasonable proxy for the disfigurement associated with LSCD. The utility decrement associated with cataract disfigurement is smaller than the

decrement associated with LSCD disfigurement and clinical advice was that disfigurement with LSCD can be worse than with cataracts although as stated earlier there will be a range of levels of disfigurement with LSCD. However, the decrement associated with cataracts also includes a loss of utility from both disfigurement and vision loss and so the utility decrement for cataract is already higher than just for the disfigurement alone. However, the ERG accepts clinical expert advice that disfigurement is a concern to patients with LSCD and so has used the full 0.140 decrement for cataracts to represent the disfigurement decrement for patients with LSCD in the base case model. The ERG considers that whilst this may still be an inaccurate estimate of the true disfigurement utility and is also a single disutility to cover a diverse range of potential disfigurement, it is a more appropriate choice both on the grounds of plausibility (it is in line with an eye condition that produces similar if not potentially as severe visual disfigurement) and also on robustness (it is derived from a UK population that actually experiences the condition).

Using the 0.140 utility decrement for disfigurement decreases the QALY gain from Holoclar in the unilateral case from 2.36 to 1.31 versus Lr-CLAL with the ICER increasing to £12,960 per QALY gained. Versus KLAL, the QALY gain decreases from 2.29 to 1.26 with the ICER increasing to £4,107 per QALY gained. Versus BSC, the QALY gain decreases from 4.91 to 3.10 with Holoclar still dominating BSC. Holoclar remains dominated by CLAU although the QALY gain with CLAU decreases from 0.55 to 0.31.

In the bilateral case, QALY gain decreases from 2.89 to 1.90 versus Lr-CLAL with the ICER increasing to £18,890 per QALY gained. Versus KLAL, the QALY gain decreases from 2.69 to 1.63 with the ICER increasing to £10,762 per QALY gained. Versus BSC, the QALY gain decreases from 6.81 to 5.07 with Holoclar still dominating BSC. There is no comparison of Holoclar versus CLAU.

Applying the VA utility values and cataract utility decrement (as discussed) in the company model changes the range of utility values produced by the model from 0.463 (unilateral patient with disfigurement and poor vision) to 0.861 (unilateral patient with 0.6 to 1.0 vision in both eyes) and successful keratoplasty (essentially returned to full or almost full health). These are utilities that are in line with the population norms for the upper utility value and for the lower value in line with the worst health states in the chronic open angle glaucoma guideline.[87]

It is noted that the utility value for successful keratoplasty – whether the ERG value (0.140) or the value used in the company model (0.318) – assumes that the disfigurement disutility is only due to disfigurement that can be rectified 100% by keratoplasty. If the disfigurement disutility is related to damage around the eye socket or parts of the eye untreated by

keratoplasty, then this assumption does not hold and the utility value and QALY gain from successful transplant and keratoplasty would not be so great.

Using the Brown 2003[92] VA utility values and the 0.140 utility decrement for disfigurement decreases the QALY gain from Holoclar in the unilateral case from 2.36 to 1.19 versus Lr-CLAL with the ICER increasing to £14,291 per QALY gained. Versus KLAL, the QALY gain decreases from 2.29 to 1.15 with the ICER increasing to £4,494 per QALY gained. Versus BSC, the QALY gain decreases from 4.91 to 2.52 with Holoclar still dominating BSC. Holoclar remains dominated by CLAU although the QALY gain with CLAU decreases from 0.55 to 0.28.

In the bilateral case, QALYs decrease from 2.89 to 1.60 versus Lr-CLAL with the ICER increasing to £22,524 per QALY gained. Versus KLAL, QALYs decrease from 2.69 to 1.28 with the ICER increasing to £13,702 per QALY gained. Versus BSC, QALYs decrease from 6.81 to 3.60 with Holoclar still dominating BSC. There is no comparison of Holoclar versus CLAU.

The company also applied a utility decrement for pain/burning/photophobia in the model using the EQ-5D norms: Level 2 pain for moderate pain and Level 3 pain for severe pain. In the absence of directly collected EQ-5D data from patients with LSCD, the ERG considers this approach to be reasonable and notes that the actual decrements applied to each health state are small and do not exceed 0.02. However, the company assumes that any pain/burning/photophobia experienced by patients is for life unless the transplant is successful. The ERG considers that this assumption is potentially implausible although accepts that the true position is unknown. To explore the importance of the pain decrement, the ERG estimated the impact on the size of the ICER per QALY gained through a scenario analysis (i.e. removal of the pain decrement) and found that it made only a very small impact on incremental QALYs of between 0.01 and 0.02 and so did not consider that this was significant enough to alter in the model.

### 5.4.3 Discount rate

The company has applied a discount rate of 1.5% pa to both costs and benefits. The Appraisal Committee may consider using a discount rate of 1.5% pa instead of the NICE standard Reference Case discount rate of 3.5% pa if the following condition from the NICE Guide to the Methods of Technology Appraisal[54] is met:

*In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be*

*considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. (Section 6.2.19)*

The ERG considers that the technology presented in this submission does not extend life or affect a cure for terminal disease and as such the first clause in the above condition does not apply.

HRQoL is impaired by moderate to severe LCSD. However, the extent of the severity is unknown. In addition, whether Holoclar, or any of the other interventions considered in this appraisal, is able to remove this impairment and result in patients being at or near full health is also unknown.

An assessment of the severity of the condition is ultimately subjective in the absence of any actual HRQoL data from patients with moderate to severe LCSD due to ocular burns. The utility evidence described in Section 5.4.2 suggests that there is a reasonable HRQoL loss particularly associated with disfigurement. On balance, the ERG considers that taking into account evidence from clinical experts, who consider that this disfigurement is severe, the loss in utility for this group of patients - even if just 0.140 as assumed in the ERG amendment – is significant and of concern to this group of patients.

The issue then is whether the procedures under consideration in this appraisal raise HRQoL back to full or near full health for this group of patients. The ERG considers this is not the case for the majority of patients with moderate to severe LSCD due to ocular burns who undergo treatment with Holoclar or any of the other procedures.

As stated in the CS, this is a patient group that often has other serious co-morbidities related to the incident that caused the LSCD. As such, even if the eye damage was fully rectified, some of these patients would not be restored to full or near full health. Even in patients that have no other co-morbidities with unilateral LSCD, the company model estimates that 76.6% have transplant success with Holoclar. Of these, 50.5% will not have stromal scarring and so will maintain the utility decrement for disfigurement. Thus, only 38.6% of all patients treated with Holoclar will have no disfigurement after treatment. Of those 38.6%, only 25% will have a ‘good’ level of VA in the operated eye with the majority of these patients having good VA in the eye before the operation. The majority of patients without disfigurement do not therefore have their vision restored beyond a poor or average level of VA (where ‘average’ is for the patient group not for the population as a whole).

Holoclar and the other procedures considered in the CS do appear to offer the hope of a return to near or full health for individuals whose only HRQoL issue is due to LSCD, which is both severe in disfigurement and in VA. However, for most individuals the procedures can only

improve HRQoL rather than come close to restoring it nearly or fully. As such, the ERG considers that the appropriate discount rate to use in the model is 3.5% pa.

Using a 3.5% pa discount rate for costs and benefits in the unilateral case increases the ICER for Holoclar versus Lr-CLAL to £21,182 per QALY gained. Versus KLAL, the ICER increases to £15,245 per QALY gained. Versus BSC, Holoclar no longer dominates and ICER is £3,563 per QALY gained. Holoclar remains dominated by CLAU although the QALY gain with CLAU decreases from 0.55 to 0.41 and the incremental cost of Holoclar decreases to £69,491.

In the bilateral case, the ICER for Holoclar versus Lr-CLAL increases to £34,817 per QALY gained. Versus KLAL the ICER increases to £29,818 per QALY gained. Versus BSC, Holoclar no longer dominates BSC and the ICER is £6,708 per QALY gained. There is no comparison of Holoclar versus CLAU.

This is a key finding for patients with bilateral LSCD treated in both eyes with Holoclar. As stated previously, there is no argument that, if the company utility values are true, then applying a 1.5% pa discount rate to costs and benefits is inappropriate. However, under the company base case assumptions, the mean utility for a stable successful Holoclar transplant is just 0.42 which cannot be considered as 'close to full health'. So, even if the assumption made by the company that the efficacy associated with bilateral and unilateral transplants is the same and all of the parameters employed by the company for resource use and utility reflect reality, the 3.5% pa discount rate should be applied as patients are not restored to 'close to full health'. The ICERs for Holoclar would then be at or exceed £30,000 per QALY gained when Holoclar is compared to Lr-CLAL and KLAL for patients with bilateral LSCD treated in both eyes.

The reason for the marked increase in the size of the ICERs per QALY gained is largely due to the decrease in the incremental QALY benefits from Holoclar. With a higher discount rate, the QALY benefits from Holoclar are now more heavily discounted than they were previously. In addition, as the majority of the costs of Holoclar are up front (mostly incurred in the first year and therefore are largely undiscounted), the costs of BSC and failed transplant exist in the future; this means that a higher discount rate reduces the costs of BSC and failed transplant more than it reduces the costs of Holoclar.

### 5.4.4 Use of autologous serum eye drops

The ERG has reviewed the cost and resource use assumptions and values used in the company's economic models. Clinical expert advice to the ERG is that there are a number of aspects related to cost and resource use in the company models that would not be relevant to the use of Holoclar (or the other procedures) in the NHS. For example, the ERG's clinical experts do not accept the company's assumptions about the use of bandage contact lenses

and the need for ophthalmic outpatient appointments. However, any changes to these parameters only influence the size of the ICER per QALY gained by less than 1% and so are considered to be minor and are not included in the ERG's amendments table.

More importantly, a difference in opinion between clinical experts exists for the use of autologous serum eye drops. In two key areas the changes recommended by the ERG have a significant impact on the size of the estimated incremental costs between procedures.

**The use of autologous serum eye drops post-operatively**

In the company model it is assumed that patients use autologous serum eye drops for a 3-month period after all procedures except for Holoclar. It was stated in the CS (p32) and in response to a clarification question from the ERG (REF CQ B5) that this was because, in the SmPC[30] and clinical study reports of Holoclar,[41-43,50] autologous serum eye drops were not reported to be used post-operatively. Clinical advice to the company was that these eye drops are however used post-operatively for CLAU, Lr-CLAL and KLAL.

There are no clinical guidelines on the post-operative use of autologous serum eye drops and all of the transplant procedures into the recipient eye are essentially identical. The ERG therefore considers it unlikely that a surgeon currently using autologous serum eye drops with CLAU, Lr-CLAL or KLAL will not use autologous serum eye drops should they start to treat patients using Holoclar. Conversely, if a surgeon is not currently using autologous serum eye drops with CLAU, Lr-CLAL or KLAL, they would not then use them for Holoclar. In either case, the ERG considers that autologous serum eye drops should be used for all procedures or for none of the procedures considered in the company model. Adding or removing a cost that is the same for all procedures makes no difference to the size of the incremental costs estimated between procedures; adding the cost of post-operative autologous serum eye drops to Holoclar or removing the cost from the alternative procedures has equal effect on the size of the ICER per QALY gained. The ERG has therefore added the cost to Holoclar.

In the unilateral case, when comparing Holoclar versus Lr-CLAL, using serum eye drops for all procedures post-operatively increases the incremental costs from £[redacted] to £[redacted] with the ICER increasing to £8,129 per QALY gained. Versus KLAL, incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £3,239 per QALY gained. Holoclar continues to dominate BSC. Holoclar remains dominated by CLAU although the incremental costs increase from £[redacted] to £[redacted].

In the bilateral case, for the comparison of Holoclar versus Lr-CLAL, incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £13,923 per QALY gained. Versus KLAL, incremental costs increase from £[redacted] to £[redacted]

[redacted] with the ICER increasing to £8,130 per QALY gained. Versus BSC, Holoclar is no longer cost saving and there are additional costs of £[redacted] with an ICER of £351 per QALY gained. There is no comparison of Holoclar versus CLAU.

**The use of autologous serum eye drops for flare-up**

In the company model it is assumed that two flare-ups per year occur for patients with LSCD either on BSC or after transplant failure. During each flare-up the patient is provided with autologous serum eye drops. In the company base case, autologous serum eye drops for flare-up account for £[redacted] (88.0%) of the cost of BSC, £[redacted] (76.5%) of the cost of Lr-CLAL and £[redacted] (61.0%) of the cost of KLAL but account for only £[redacted] (21.7%) of the cost of Holoclar. The actual number of flare-ups and the frequency of use of autologous serum eye drops are by far the biggest drivers of costs in the company model for Lr-CLAL, KLAL and BSC.

The company has based the use of autologous serum eye drops on the advice of clinicians who were presented with a list of products (including autologous serum eye drops) that could be used to treat flare-ups. The responses from the clinicians were that all of the products could be used at some stage, with one clinician estimating the cost of BSC to be £[redacted] per year. However, the ERG sought clinical advice on the use of autologous serum eye drops for flare-up and was informed that they were not routinely used in the NHS. Part of the problem with this treatment is that it can take 4 weeks to manufacture autologous serum eye drops (http://hospital.blood.co.uk/media/2136/84065ff9-6ce6-422e-99ed-b9dd86393cb6.pdf) and if flare-ups happen they may resolve before the eye drops are manufactured. Again, it seems that clinical practice varies by surgeon.

The ERG is of the opinion that, due to the lack of clarity on the use of autologous serum eye drops when used to treat patients with flare-ups, two scenarios (i.e., treatment with and without the use of autologous serum drops for flare-ups) must be considered.

The company base case model includes the use of serum autologous eye drops.

An ERG amendment therefore considers the impact on the size of the ICER per QALY gained when autologous serum eye drops are **not** used to treat flare-ups in the unilateral case. When comparing Holoclar with Lr-CLAL, the incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £23,328 per QALY gained. Versus KLAL, incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £16,766 per QALY gained. Versus BSC, Holoclar is no longer cost saving and there are now additional costs of £[redacted] with an ICER of £12,467 per QALY gained. Holoclar remains dominated by CLAU, although the incremental costs decrease from £[redacted] to £[redacted].

In the bilateral case, incremental costs increase from £[redacted] to £[redacted] versus Lr-CLAL with the ICER increasing to £37,138 per QALY gained. Versus KLAL, incremental costs increase from £[redacted] to £[redacted] with the ICER increasing to £28,237 per QALY gained. Versus BSC, Holoclar is no longer cost saving and there is now an additional cost of £[redacted] with an ICER of £18,980 per QALY gained. There is no comparison of Holoclar versus CLAU.

### 5.4.5 Use of KLAL after failure with Lr-CLAL

The company has assumed that patients are only eligible for one type of procedure for their LSCD. In practice, the ERG considers it is not unlikely that a second living relative donation for Lr-CLAL may be available from the living relative who provided the first donation as cells can also be taken from the other eye. Indeed, this is the implicit assumption that permits the use of Lr-CLAL to treat both eyes of a patient with bilateral LSCD. It is also unlikely that whilst patients can have up to three KLAL transplants they will not be eligible for KLAL should Lr-CLAL fail.

The ERG therefore considers that a more plausible scenario is to allow patients with unilateral LSCD to undergo at least two attempts with Lr-CLAL; this can be interpreted as two genuine attempts at Lr-CLAL or as a proxy for one attempt with Lr-CLAL and one attempt with KLAL as the costs and effectiveness of both treatments are broadly comparable.

For bilateral patients, the ERG has assumed that only one attempt will be made with Lr-CLAL. If only one relative comes forward to donate cells then donations from both eyes are required to treat the two damaged eyes of the patient and so therefore the relative would not be able to donate again should either transplant fail. However, it is possible that the patient could be eligible for KLAL; this is another reason that the bilateral results need to be treated with caution.

Allowing Lr-CLAL to be used twice increases both the incremental cost of Holoclar over Lr-CLAL (from £[redacted] to £[redacted]) whilst reducing the QALY gain from 2.36 to 1.12. This has the effect of increasing the size of the ICER to £30,415 per QALY gained.

# 6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

This section summarises the impact of the ERG's amendments to the company's models when Holoclar is compared to CLAU, Lr-CLAL, KLAL and BSC in patients with unilateral moderate to severe LSCD and when Holoclar is compared to Lr-CLAL, KLAL and BSC in patients with bilateral moderate to severe LSCD.

The ERG has only considered the changes in the model that would have a major impact on the size of the ICERs and has not considered the minor issues described in Section 5 (e.g., the slight implausibility of the pain decrement and the difference in clinical opinion on frequency of outpatient appointments).

## *6.1 Unilateral LSCD (Table 33 to Table 36)*

For patients with unilateral LSCD, whilst most of the amendments made by the ERG reduce the cost and QALY differential when Holoclar is compared to CLAU, in all cases CLAU remains the dominant strategy generating more QALYs than Holoclar at a lower cost.

For Lr-CLAL and KLAL the ERG amendments increase the ICER to £152,590 per QALY gained and £33,473 per QALY gained respectively if autologous serum eye drops continue to be used for flare-ups. If autologous serum eye drops are not used routinely for flare-ups as suggested by clinical advice to the ERG, then the ICERs increase further to £179,066 per QALY gained for Holoclar compared to Lr-CLAL and to £60,996 for Holoclar compared to Lr-CLAL. Even if Lr-CLAL is only used once in practice, with no opportunity for a second procedure on failure be it Lr-CLAL or KLAL, then the ICER would still increase to £45,048 per QALY gained if autologous serum eye drops were routinely used for flare-ups and £76,963 per QALY gained if they were not routinely used for flare-ups.

Compared to BSC, the ERG amendments show Holoclar continues to dominate or have an ICER no higher than £12,500 per QALY gained unless all of the ERG amendments were taken into account with autologous serum eye drops **not** being routinely used for flare-ups. In this case, the ICER for Holoclar compared to BSC is £35,489 per QALY gained.

## *6.2 Bilateral LSCD (Table 37 to Table 39)*

For patients with bilateral LSCD, when Holoclar is compared to Lr-CLAL, simply applying a 3.5% pa discount rate to costs and benefits increases the ICER to £34,817 per QALY gained. If all of the ERG amendments are implemented then the ICER increases to £67,219 per QALY gained if autologous serum eye drops are routinely used for flare-ups and to £111,654 per QALY gained if they are not. These ICERs are based on the assumption that patients with bilateral LSCD would not be eligible for KLAL if Lr-CLAL failed.

When Holoclar is compared to KLAL, applying the 3.5% pa discount rate to costs and benefits increases the ICER to £29,818 per QALY gained. If all the ERG amendments are implemented then the ICER increases to £75,457 per QALY gained if autologous serum eye drops are routinely used for flare-ups and to £122,468 per QALY gained if they are not.

When Holoclar is compared with BSC, the ERG amendments show that Holoclar continues to dominate or has an ICER no higher than £19,000 per QALY gained unless all of the ERG amendments are implemented with autologous serum eye drops **not** being routinely used for flare-ups. In this case, the ICER for Holoclar compared to BSC is £50,973 per QALY gained.

There is no comparison of Holoclar versus CLAU.

Table 33 ERG adjustments to company base case: Holoclar versus CLAU (unilateral model)

| *Scenario/ERG amendment* | Holoclar | | CLAU | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | **£[redacted]** | ***12.09*** | ***£22,158*** | ***12.64*** | [redacted] | ***-0.55*** | ***Dominated*** | |
| R1) Use of Brown 2003 VA utility values | £[redacted] | 16.43 | £22,158 | 16.95 | [redacted] | -0.52 | Dominated | - |
| R2) ERG preferred decrement for disfigurement | £[redacted] | 15.11 | £22,158 | 15.41 | [redacted] | -0.31 | Dominated | |
| **B. ERG preferred utility scenario (R1+R2)** | **£[redacted]** | **19.44** | **£22,158** | **19.72** | [redacted] | **-0.28** | **Dominated** | |
| R3) 3.5% discount rate | £[redacted] | 8.93 | £18,651 | 9.34 | [redacted] | -0.41 | Dominated | |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | **£[redacted]** | **14.40** | **£18,651** | **14.60** | [redacted] | **-0.21** | **Dominated** | |
| R4) Autologous serum eye drops post-operatively with Holoclar | £[redacted] | 12.09 | £22,158 | 12.64 | [redacted] | -0.55 | Dominated | |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | **£[redacted]** | **14.40** | **£18,651** | **14.60** | [redacted] | **-0.21** | **Dominated** | |
| R5) Autologous serum eye drops not used in flare-ups | £[redacted] | 12.09 | £10,358 | 12.64 | [redacted] | -0.55 | Dominated | |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of autologous serum eye drops for flare-ups (R1-R5)** | **£[redacted]** | **14.40** | **£9,901** | **14.60** | [redacted] | **-0.21** | **Dominated** | |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; CLAU=conjunctival limbal autograft

Table 34 ERG adjustments to company base case: Holoclar versus Lr-CLAL (unilateral model)

| *Scenario/ERG amendment* | Holoclar | | Lr-CLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***12.09*** | ***£77,434*** | ***9.73*** | [redacted] | ***2.36*** | ***£7,185*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 16.43 | £77,434 | 14.18 | [redacted] | 2.24 | £7,576 | £391 |
| R2) ERG preferred decrement for disfigurement | [redacted] | 15.11 | £77,434 | 13.79 | [redacted] | 1.31 | £12,960 | £5,775 |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **19.44** | **£77,434** | **18.25** | [redacted] | **1.19** | **£14,291** | **£7,106** |
| R3) 3.5% discount rate | [redacted] | 8.94 | £55,782 | 7.41 | [redacted] | 1.53 | £21,182 | £13,998 |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **14.40** | **£55,782** | **13.63** | [redacted] | **0.77** | **£42,139** | **£34,954** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 12.09 | £77,434 | 9.73 | [redacted] | 2.36 | £8,129 | £945 |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **14.40** | **£55,782** | **13.63** | [redacted] | **0.77** | **£45,048** | **£37,863** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 12.09 | £18,222 | 9.73 | [redacted] | 2.36 | £23,328 | £16,143 |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **14.40** | **£15,587** | **13.63** | [redacted] | **0.77** | **£76,963** | **£69,778** |
| R6) Two attempts at Lr-CLAL | [redacted] | 12.10 | £60,373 | 10.97 | [redacted] | 1.12 | £30,415 | £23,230 |
| **F. All suggested changes from ERG but continued use of autologous serum eye drops for flare-up (R1-R4, R6)** | [redacted] | **14.40** | **£43,805** | **14.09** | [redacted] | **0.31** | **£152,590** | **£145,405** |
| **G. All suggested changes from ERG (R1-R6)** | [redacted] | **14.40** | **£20,038** | **14.09** | [redacted] | **0.31** | **£179,066** | **£171,881** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; Lr-CLAL=conjunctival limbal allograft from a live related donor

Table 35 ERG adjustments to company base case: Holoclar versus KLAL (unilateral model)

| *Scenario/ERG amendment* | Holoclar | | KLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***12.09*** | ***£89,256*** | ***9.80*** | [redacted] | ***2.29*** | ***£2,255*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 16.43 | £89,256 | 14.24 | [redacted] | 2.18 | £2,367 | £112 |
| R2) ERG preferred decrement for disfigurement | [redacted] | 15.11 | £89,256 | 13.85 | [redacted] | 1.26 | £4,107 | £1,852 |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **19.44** | **£89,256** | **18.29** | [redacted] | **1.15** | **£4,494** | **£2,240** |
| R3) 3.5% discount rate | [redacted] | 8.93 | £65,932 | 7.48 | [redacted] | 1.46 | £15,245 | £12,990 |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **14.40** | **£65,932** | **13.67** | [redacted] | **0.73** | **£30,415** | **£28,160** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 12.09 | £89,256 | 9.80 | [redacted] | 2.29 | £3,239 | £975 |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **14.40** | **£65,932** | **13.67** | [redacted] | **0.73** | **£33,473** | **£31,219** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 12.09 | £34,960 | 9.80 | [redacted] | 2.29 | £16,766 | £14,512 |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **14.40** | **£30,147** | **13.67** | [redacted] | **0.73** | **£60,996** | **£58,741** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; KLAL=keratolimbal allograft

Table 36 ERG adjustments to company base case: Holoclar versus BSC (unilateral model)

| *Scenario/ERG amendment* | Holoclar | | BSC | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***12.09*** | ***£101,535*** | ***7.18*** | [redacted] | ***4.91*** | ***Dominates*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 16.43 | £101,535 | 12.10 | [redacted] | 4.33 | Dominates | - |
| R2) ERG preferred decrement for disfigurement | [redacted] | 15.11 | £101,535 | 12.01 | [redacted] | 3.10 | Dominates | - |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **19.44** | **£101,535** | **16.92** | [redacted] | **2.52** | **Dominates** | **-** |
| R3) 3.5% discount rate | [redacted] | 8.93 | £75,289 | 5.33 | [redacted] | 3.61 | £3,563 | - |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **14.40** | **£75,289** | **12.55** | [redacted] | **1.85** | **£6,948** | **-** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 12.09 | £101,535 | 7.18 | [redacted] | 4.91 | Dominates | - |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **14.40** | **£75,289** | **12.55** | [redacted] | **1.85** | **£8,155** | **-** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 12.09 | £12,188 | 7.18 | [redacted] | 4.91 | £12,467 | - |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **14.40** | **£9,037** | **12.55** | [redacted] | **1.85** | **£35,489** | **-** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; BSC=best supportive care, ERG=Evidence Review Group; BSC=best supportive care

Table 37 ERG adjustments to company base case: Holoclar versus Lr-CLAL (bilateral model)

| *Scenario/ERG amendment* | Holoclar | | Lr-CLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***9.25*** | ***£155,430*** | ***6.36*** | [redacted] | ***2.89*** | ***£12,438*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 13.05 | £155,430 | 10.47 | [redacted] | 2.59 | £13,916 | £1,478 |
| R2) ERG preferred decrement for disfigurement | [redacted] | 12.34 | £155,430 | 10.43 | [redacted] | 1.90 | £18,890 | £6,452 |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **16.14** | **£155,430** | **14.54** | [redacted] | **1.60** | **£22,524** | **£10,086** |
| R3) 3.5% discount rate | [redacted] | 6.77 | £112,364 | 4.93 | [redacted] | 1.85 | £34,817 | £22,379 |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **11.93** | **£112,364** | **10.91** | [redacted] | **1.02** | **£63,047** | **£50,609** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 9.25 | £155,430 | 6.36 | [redacted] | 2.89 | £13,923 | £1,485 |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **11.93** | **£112,364** | **10.91** | [redacted] | **1.02** | **£67,219** | **£54,781** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 9.25 | £36,358 | 6.36 | [redacted] | 2.89 | £37,138 | £24,700 |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **11.93** | **£30,948** | **10.91** | [redacted] | **1.02** | **£111,654** | **£99,216** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; Lr-CLAL=conjunctival limbal allograft from a live related donor

Table 38 ERG adjustments to company base case: Holoclar versus KLAL (bilateral model)

| *Scenario/ERG amendment* | Holoclar | | KLAL | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| ***A. Company's base case*** | [redacted] | ***9.25*** | ***£173,844*** | ***6.56*** | [redacted] | ***2.69*** | ***£6,533*** | |
| R1) Use of Brown 2003 VA utility values | [redacted] | 13.05 | £173,844 | 10.71 | [redacted] | 2.34 | £7,512 | £979 |
| R2) ERG preferred decrement for disfigurement | [redacted] | 12.34 | £173,844 | 10.70 | [redacted] | 1.63 | £10,762 | £4,229 |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **16.14** | **£173,844** | **14.86** | [redacted] | **1.28** | **£13,702** | **£7,169** |
| R3) 3.5% discount rate | [redacted] | 6.77 | £127,407 | 5.12 | [redacted] | 1.65 | £29,818 | £23,285 |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **11.93** | **£127,407** | **11.22** | [redacted] | **0.71** | **£69,455** | **£62,922** |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 9.25 | £173,844 | 6.56 | [redacted] | 2.69 | £8,130 | £1,597 |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **11.93** | **£127,407** | **11.22** | [redacted] | **0.71** | **£75,457** | **£68,924** |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 9.25 | £67,855 | 6.56 | [redacted] | 2.69 | £28,237 | £21,704 |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **11.93** | **£57,970** | **11.22** | [redacted] | **0.71** | **£122,468** | **£115,935** |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; KLAL= keratolimbal allograft

Table 39 ERG adjustments to company base case: Holoclar versus BSC (bilateral model)

| *Scenario/ERG amendment* | Holoclar | | BSC | | Incremental | | *ICER* | |
|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | Cost | QALYs | Cost | QALYs | £ per QALY gained | Change from base case |
| **A. Company's base case** | [redacted] | **9.25** | **£193,323** | **2.44** | [redacted] | **6.81** | **Dominates** | - |
| R1) Use of Brown 2003 VA utility values | [redacted] | 13.05 | £193,323 | 7.72 | [redacted] | 5.33 | Dominates | - |
| R2) ERG preferred decrement for disfigurement | [redacted] | 12.34 | £193,323 | 7.26 | [redacted] | 5.07 | Dominates | - |
| **B. ERG preferred utility scenario (R1+R2)** | [redacted] | **16.14** | **£193,323** | **12.54** | [redacted] | **3.60** | **Dominates** | - |
| R3) 3.5% discount rate | [redacted] | 6.77 | £143,350 | 1.81 | [redacted] | 4.96 | £6,708 | - |
| **C. ERG preferred utility scenario and 3.5% discount rate (R1-R3)** | [redacted] | **11.93** | **£143,350** | **9.30** | [redacted] | **2.63** | **£12,669** | - |
| R4) Autologous serum eye drops post-operatively with Holoclar | [redacted] | 9.25 | £193,323 | 2.44 | [redacted] | 6.81 | £351 | - |
| **D. ERG preferred utility scenario, 3.5% discount rate and use of autologous serum eye drops post-operatively (R1-R4)** | [redacted] | **11.93** | **£143,350** | **9.30** | [redacted] | **2.63** | **£14,288** | - |
| R5) Autologous serum eye drops not used in flare-ups | [redacted] | 9.25 | £14,629 | 2.44 | [redacted] | 6.81 | £18,980 | - |
| **E. ERG preferred utility scenario, 3.5% discount rate, post-operative use of eye drops and no use of eye drops for flare-ups (R1-R5)** | [redacted] | **11.93** | **£10,847** | **9.30** | [redacted] | **2.63** | **£50,973** | - |

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ERG=Evidence Review Group; BSC=best supportive care

## 6.3 Conclusions of the ERG's cost effectiveness review

The ERG considers that there are several fundamental issues that cast doubt on the cost effectiveness of Holoclar versus all comparators.

First, the results of the company's base case unilateral model demonstrate that Holoclar is more expensive and less effective than CLAU. All, except one, of the amendments recommended by the ERG decrease the costs and benefits associated with Holoclar, reduce the incremental costs and increase the incremental benefits estimated when comparing Holoclar versus CLAU. Even if CLAU and Holoclar were to have the same rate of transplant success CLAU would still dominate Holoclar; CLAU is a significantly less costly procedure than Holoclar. If CLAU is currently used to treat patients with unilateral LSCD in the NHS, then the cost effectiveness evidence presented by the company suggests that failing to use CLAU in favour of any of the alternatives, including Holoclar, would generate worse patient outcomes at a higher cost.

Second, the clinical effectiveness evidence base for all of the procedures is weak as most of the data available are derived from case series studies. Case series studies by design yield low quality evidence even if well conducted. The effectiveness data for the comparators is drawn from a pooling of data from case series studies; in the CS the company claimed that pooling would be inappropriate due to parameter heterogeneity. The ERG agrees that it is inappropriate to pool these data but considers that use of the pooled data in the model generates no less robust results than the arbitrary selection of data from one of the small case series studies. However, the weakness of the underlying data – pooled or otherwise - casts significant doubt on the robustness of the ICERs per QALY gained built upon these data.

Third, the clinical effectiveness evidence provided by the company to support the use of Holoclar to treat both eyes in patients with bilateral LSCD is limited to data describing one patient. Given there are plausible clinical reasons as to why Holoclar may not be as effective when used to treat bilateral LSCD compared with use in unilateral LSCD, the ERG considers that the cost effectiveness results from the bilateral model are of extremely limited value to the point of being non-informative.

Fourth, the ERG considers that the utility values incorporated into the company models were implausibly low and the disutility value used for disfigurement was implausibly high. The ERG therefore used more plausible utility values in the model and these changes had substantial impacts on the size of the ICERs per QALY gained.

Fifth, the discount rate applied by the company should be 3.5% pa rather than 1.5% pa. NICE only permits the use of a lower discount rate if an intervention cures terminal illness or removes a significant detriment to HRQoL such that a patient lives at or near full health for the remainder

of their life. The ERG considers that neither of these clauses applies to treatment with Holoclar. In the bilateral model, simply applying the 3.5% pa discount rate increases the size of the ICER per QALY gained; the ICER for Holoclar versus Lr-CLAL is £34,849 per QALY gained and the ICER for Holoclar versus KLAL is £29,852 per QALY gained.

Sixth, there is some doubt about where the use of autologous serum eye drops sits in the treatment pathway, especially when used to treat patients with flare-ups. As the cost of using these eye drops to treat flare-ups accounts for the majority of the cost of BSC – which patients with failed transplants move onto – accurate costing of their use significantly affects the size of the ICER per QALY gained.

Seventh, the ERG considers it implausible that patients with unilateral LSCD who fail after Lr-CLAU are not offered a second procedure.

Finally, the models were not designed to include failure rates beyond 12 months after a successful transplant. This is an issue for the evaluation of CLAU where clinical advice provided to the company suggested that failure rates at 10 years could be as high as 30%. This in turn becomes an issue for Holoclar where real world transplant success rates at 10 years are essentially non-existent; if stable transplants for CLAU can fail many years after successful transplant this could also be the case for Holoclar. If CLAU and Holoclar can fail post 12 months after transplant, then the models will systematically underestimate the true ICERs per QALY gained for CLAU and Holoclar compared to the alternative treatments.

In the unilateral LSCD model, application of the ERG changes to utility values, discount rates and modifications to the use of autologous serum eye drops resulted in ICERs for Holoclar remaining dominated by CLAU with an incremental cost of £[redacted] (R1-R5). Versus Lr-CLAL, the ICER is £179,066 per QALY gained (this ICER includes a second procedure after initial transplant failure, R1-R6). Versus KLAL, the ICER is £60,996 per QALY gained (R1-R5). Compared to BSC, the ICER is £35,489 per QALY gained (R1-R5).

In the bilateral LSCD model, application of the ERG changes to utility values, discount rates and modifications to the use of autologous serum eye drops resulted in ICERs for Holoclar versus Lr-CLAL of £116,654 per QALY gained (R1-R5). Versus KLAL, the ICER is £122,468 per QALY gained (R1-R5). Versus BSC, the ICER is £50,973 per QALY gained (R1-R5).

# 7 END OF LIFE

The company has not put forward a case for Holoclar to be considered under the NICE End of Life criteria. The ERG agrees that this is appropriate.

# 8 DISCUSSION

The primary source of clinical effectiveness evidence for Holoclar provided by the company is derived from a single, retrospective case series study (the HLSTM01 study) of 104 patients with LSCD due to ocular burns. LSCD due to ocular burns is a rare condition and so a study of 104 patients is a sizeable study; however, a case series study (particularly when conducted retrospectively) has an inherently weak study design and the results are descriptive rather than analytical. In the absence of an appropriate comparator arm in the HLSTM01 case series study, it is difficult to evaluate the true clinical effectiveness of Holoclar. The company was unable to identify any reliable evidence for the clinical effectiveness of any of the stated comparators to Holoclar. As a result, it was inappropriate to carry out an ITC and the evidence for the clinical effectiveness of treatment with Holoclar versus all comparators is largely reliant on the results of retrospective case series studies.

A further difficulty in the evaluation of the outcomes of the HLSTM01 study is that no HRQoL data were collected. This means that the HRQOL impact of treatment with Holoclar treatment is unknown.

The company makes the claim that Holoclar can be used to treat both eyes in patients with moderate to severe LSCD and, further, assumes that treatment of the second eye is as effective as treatment of the first eye. However, the company has not provided any clinical evidence to support either the claim or the ensuing assumption.

The treatment of LSCD due to ocular burns is a highly specialised area for which there are no agreed treatment protocols, no standard comparator treatments and no licensed treatments, other than Holoclar, are available. Lack of consensus in these areas poses problems when evaluating the cost effectiveness of Holoclar. A particular issue for this appraisal is variation in the use (or otherwise) of autologous serum eye drops as, depending on how they are used, the cost of the eye drops has a substantial impact on the size of the ICERs per QALY gained.

The company has initiated three further studies[50,95,96] of Holoclar (HOLOCORE, HOLOCORE-FU AND HOLOSIGHT) and, whilst all are multinational prospective studies, all are designed as observational studies and do not include control groups. The company discusses (CS, p72) the difficulties inherent in designing a RCT to evaluate the clinical effectiveness of Holoclar. The barriers to designing and conducting such a RCT are numerous and include ethical and practical considerations. Although the ERG agrees that a RCT of the technology would be

challenging, the ERG notes that a small RCT[49] has already been carried out in this area. The ERG cautions that studies of similar technologies to Holoclar are likely to emerge and a rigorous, standardised approach to the design and analysis of these clinical studies is needed

# 9 OVERALL CONCLUSIONS

## *9.1 Implications for research*

As there are no HRQoL data relevant to the use of Holoclar or any of the comparator treatments, studies providing HRQoL data would be welcomed. The company plans to collect HRQoL data relevant to Holoclar data from the patients recruited to the HOLOCORE,[50] HOLOCORE-FU[95,96] and the HOLOSIGHT[95] studies. The results of the first of the studies (HOLOCORE[50]) are likely to be available in 2020.

There is a lack of evidence to support the clinical effectiveness of treatment with Holoclar in patients with bilateral LSCD due to ocular burns who have both eyes treated. Future studies should collect data pertinent to treatment outcomes for these patients. The data collected should enable a comparison of treatment outcomes between the first and second treated eyes.

Further evidence of the duration of treatment beyond 1 year is also needed. The three studies[50,95,96] planned by the company are intended to collect data for up to 5 years post-transplantation.

# 10 REFERENCES


1. Chiesi Ltd. Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns [ID899]: Company evidence submission to NICE 2016.
2. Dua HS, Joseph A, Shanmuganathan VA, Jones RE. Stem cell differentiation and the effects of deficiency. Eye. 2003; 17:877-85.
3. Shaharuddin B, Ahmad S, Ali S, Meeson A. Limbal side population cells: A future treatment for limbal stem cell deficiency. Regen Med. 2013; 8:319-31.
4. Sejpal K, Bakhtiari P, Deng SX. Presentation, diagnosis and management of limbal stem cell deficiency. Middle East Afr J Ophthalmol. 2013; 20:5-10.
5. Dua HS, Miri A, Said DG. Contemporary limbal stem cell transplantation - a review. Clin Experiment Ophthalmol. 2010; 38:104-17.
6. Haagdorens M, Van Acker SI, Van Gerwen V, Ni Dhubhghaill S, Koppen C, Tassignon MJ, *et al.* Limbal stem cell deficiency: Current treatment options and emerging therapies. Stem Cells Int. 2016; 2016:9798374.
7. Hatch K, Dana R. The structure and function of the limbal stem cell and the disease states associated with limbal stem cell deficiency. Int Ophthalmol Clin. 2009; 149:43-52.
8. Osei-Bempong C, Figueiredo FC, Lako M. The limbal epithelium of the eye-a review of limbal stem cell biology, disease and treatment. BioEssays : news and reviews in molecular, cellular and developmental biology. 2013; 35:211-9.
9. Espana EM, Grueterich M, Romano AC, Touhami A, Tseng SC. Idiopathic limbal stem cell deficiency. Ophthalmology. 2002; 109:2004-10.
10. Lichtinger A, Pe'er J, Frucht-Pery J, Solomon A. Limbal stem cell deficiency after topical mitomycin C therapy for primary acquired melanosis with atypia. Ophthalmology. 2010; 117:431-7.
11. Burcu A, Yalniz-Akkaya Z, Ozdemir MF, Erdem E, Onat MM, Ornek F. Surgical rehabilitation following ocular chemical injury. Cutan Ocul Toxicol. 2014; 33:42-8.
12. Crawford AZ, McGhee CN. Management of limbal stem cell deficiency in severe ocular chemical burns. Clin Experiment Ophthalmol. 2012; 40:227-9.
13. European Medicines Agency. Assessment Report: Holoclar 2014.
14. Macdonald EC, Cauchi PA, Azuara-Blanco A, Foot B. Surveillance of severe chemical corneal injuries in the UK. Br J Ophthalmol. 2009; 93:1177-80.
15. Baylis O, Figueiredo F, Henein C, Lako M, Ahmad S. 13 years of cultured limbal epithelial cell therapy: a review of the outcomes. J Cell Biochem. 2011; 112:993-1002.
16. Bobba S, Chow S, Watson S, Di Girolamo N. Clinical outcomes of xeno-free expansion and transplantation of autologous ocular surface epithelial stem cells via contact lens delivery: a prospective case series. Stem Cell Res Ther. 2015; 6:23.
17. Graham JS, Schoneboom BA. Historical perspective on effects and treatment of sulfur mustard injuries. Chem Biol Interact. 2013; 206:512-22.
18. Shortt AJ, Tuft SJ, Daniels JT. Corneal stem cells in the eye clinic. Br Med Bull. 2011; 100:209-25.
19. Medical Advisory Secretariat. Limbal stem cell transplantation: An evidence-based analysis. Ontario Health Technology Assessment Series. 2008; 8.
20. World Health Organisation. Socio economic aspects of blindness and visual impairment. 2016; Available from: http://www.who.int/blindness/economy/en/ [accessed September 2016].
21. Chiesi Farmaceutici S.p.A. Notes from meeting with Mr Alex Shortt 22nd June 2016 (CHHOL20160794). Data on file. 2016.
22. Ramachandran C, Basu S, Sangwan VS, Balasubramanian D. Concise review: the coming of age of stem cell treatment for corneal surface damage. Stem Cells Transl Med. 2014; 3:1160-8.

23. Rao SK, Rajagopal R, Sitalakshmi G, Padmanabhan P, Rao SK, Rajagopal R*, et al.* Limbal autografting: comparison of results in the acute and chronic phases of ocular surface burns. Cornea. 1999; 18:164-71.
24. Dua S, Azuara-Blanco A. Allo-limbal transplantation in patients with limbal stem cell deficiency. Br J Ophthalmol. 1999; 83:414-9.
25. Cauchi PA, Ang GS, Azuara-Blanco A, Burr JM. A systematic literature review of surgical interventions for limbal stem cell deficiency in humans. Am J Ophthalmol. 2008; 146:251-9.
26. Miri A, Al-Deiri B, Dua HS. Long-term outcomes of autolimbal and allolimbal transplants. Ophthalmology. 2010; 117:1207-13.
27. Gomes JA, dos Santos MS, Cunha MC, Mascaro VL, Nadai Barros J, de Sousa LB. Amniotic membrane transplantation for partial and total limbal stem cell deficiency secondary to chemical burn. Ophthalmology. 2003; 110:466-73.
28. Fish R, Davidson RS. Management of ocular thermal and chemical injuries, including amniotic membrane therapy. Current Opinion in Ophthalmology. 2010; 21:317-1.
29. Ucakhan OO, Koklu G, Firat E. Nonpreserved human amniotic membrane transplantation in acute and chronic chemical eye injuries. Cornea. 2002; 21:169-72.
30. Chiesi Farmaceutici S.p.A. Summary of Product Characteristics. Holoclar.2015.
31. National Institute for Health and Care Excellence. IPG216: Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium. Interventional procedure guidance. 2007; Available from: nice.org.uk/guidance/ipg216 [accessed 31st August 2016].
32. National Institute for Health and Care Excellence. NICE Pathways: Eye conditions overview London: NICE; 2015; Available from: http://pathways.nice.org.uk/pathways/eye-conditions [accessed August 2016].
33. Department of Health. The NHS Outcomes Framework 2015/16.2014.
34. NHS England. Manual for prescribed specialised services 2013/14. 2016.
35. NHS England. NHS Standard contract for specialised ophthalmology (adult). 2016.
36. NHS England. 2013/14 NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness.2013.
37. European Medicines Agency. History of the EMA. 2016; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000628.jsp&mid=WC0b01ac058087addd [accessed Sept 2016].
38. Office for National Statistics. Annual Mid-year Population Estimates, 2014. 2015.
39. Medi-Pragma. Limbal Stem Cell Deficiency Market Potential Analysis Summary Report. 2012. Data on file.2012.
40. National Institute for Health and Care Excellence. Final scope: Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns ID899 2016.
41. Chiesi Farmaceutici S.p.A. HLSTM01 Clinical Study Report 2012.
42. Chiesi Farmaceutici S.p.A. HLSTM02 Clinical Study Report 2012.
43. Chiesi Farmaceutici S.p.A. HLSTM04 Clinical Study Report 2014.
44. Marchini G, Pedrotti E, Pedrotti M, Barbaro V, Di Iorio E, Ferrari S*, et al.* Long-term effectiveness of autologous cultured limbal stem cell grafts in patients with limbal stem cell deficiency due to chemical burns. Clinical & Experimental Ophthalmology. 2012; 40:255-67.
45. Pellegrini G, Rama P, Matuska S, Lambiase A, Bonini S, Pocobelli A*, et al.* Biological parameters determining the clinical outcome of autologous cultures of limbal stem cells. Regen Med. 2013; 8:553-67.
46. Pellegrini G, Traverso CE, Franzi AT, Zingirian M, Cancedda R, De Luca M. Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium. The Lancet. 1997; 349:990-3.
47. Rama P, Bonini S, Lambiase A, Golisano O, Paterna P, De Luca M*, et al.* Autologous fibrin-cultured limbal stem cells permanently restore the corneal surface of patients with total limbal stem cell deficiency. Transplantation. 2001; 72:1478-85.

48. Rama P, Matuska S, Paganoni G, Spinelli A, De Luca M, G. P. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med. 2010; 363:147-55.
49. Titiyal JS, Sharma N, Agarwal AK, Prakash G, Tandon R, Vajpayee R. Live related versus cadaveric limbal allograft in limbal stem cell deficiency. Ocul Immunol Inflamm. 2015; 23:232-9.
50. Chiesi Farmaceutici S.p.A. HOLOCORE: Clinical Study Protocol 2015.
51. Chiesi Farmaceutici S.p.A. Clinical Expert Opinion Questionnaire (CHHOL20160798). Data on file. 2016.
52. Basu S, Sureka SP, Shanbhag SS, Kethiri AR, Singh V, Sangwan VS. Simple limbal epithelial transplantation: Long-term clinical outcomes in 125 cases of unilateral chronic ocular surface burns. Ophthalmology. 2016; 123:1000-10.
53. Dickinson A, Lako M, Kolli S, Figueiredo FC. Outcomes of ex-vivo expanded limbal stem cell transplantation in humans. Cytotherapy. 2013; 15:S44-5.
54. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013; Available from: http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf (Accessed 01/06/2015).
55. National Institute for Health and Care Excellence (NICE). Single technology appraisal: User guide for company evidence submission template. 2015; Available from: https://www.nice.org.uk/article/pmg24/resources/non-guidance-single-technology-appraisal-user-guide-for-company-evidence-submission-template-pdf. [accessed April 2016].
56. The Joanna Briggs Institute. Joanna Briggs Institute Reviewers' Manual: 2016 edition. Australia: The Joanna Briggs Institute; 2016; Available from: http://joannabriggs.org/research/critical--appraisal--tools.html [accessed 31st August 2016].
57. Carey TS, Boden SD. A critical guide to case series reports. Spine (Phila Pa 1976). 2003:1631-4.
58. Kooistra B, Dijkman B, Einhorn TA, Bhandari M. How to design a good case series. The Journal of Bone and Joint Surgery. 2009; 91:Suppl 3 21-6.
59. Anderson DF. Amniotic membrane transplantation for partial limbal stem cell deficiency. Br J Ophthalmol. 2001; 85:567-75.
60. Borderie V, Touzeau O, Bourcier T, Allouch C, Scheer S, Laroche L. Treatment of the sequelae of ocular burns using limbal transplantation. Journal Français d'Opthalmologie. 2003; 26:710-6.
61. Dua HS. The conjunctiva in corneal epithelial wound healing. Br J Ophthalmol. 1998; 82:1407-11.
62. Dua HS, Azuara-Blanco A. Autologous limbal transplantation in patients with unilateral corneal stem cell deficiency. Br J Ophthalmol. 2000; 84:273-8.
63. Eslani M, Baradaran-Rafii A, Movahedan A, Moss A, Holland E, Djalilian A. Late acute graft rejection after keratolimbal allograft. American Academy of Ophthalmology. 2015:PO051.
64. Fernandes M, Sangwan V, Rao S, Basti S, Sridhar M, Bansal A*, et al.* Limbal stem cell transplantation. Indian J Ophthalmol. 2004; 52:5-22.
65. Han ES, Wee WR, Lee JH, Kim MK. Long-term outcome and prognostic factor analysis for keratolimbal allografts. Graefes Arch Clin Exp Ophthalmol. 2011; 249:1697-704.
66. Holland EJ. Epithelial transplantation for the management of severe ocular surface disease. Trans Am Ophthalmol Soc. 1996; 94:677-743.
67. Huang T, Wang Y, Zhang H, Gao N, Hu A. Limbal allografting from living-related donors to treat partial limbal deficiency secondary to ocular chemical burns. Arch Ophthalmol. 2011; 129:1267-73.
68. Ilari L, Daya SM. Long-term outcomes of keratolimbal allograft for the treatment of severe ocular surface disorders. Ophthalmology. 2002; 109:1278-84.

69. Ivekovic R, Tedeschi-Reiner E, Novak-Laus K, Andrijevic-Derk B, Cima I, Mandic Z. Limbal graft and/or amniotic membrane transplantation in the treatment of ocular burns. Ophthalmologica. 2005; 219:297-302.
70. Kenyon KR, Tseng SC. Limbal autograft transplantation for ocular surface disorders. Ophthalmology. 1989; 96:709-22.
71. Kheirkhah A, Johnson DA, Paranjpe DR, Raju VK, Casas V, Tseng SC. Temporary sutureless amniotic membrane patch for acute alkaline burns. Arch Ophthalmol. 2008; 126:1059-66.
72. Maruyama-Hosoi F, Shimazaki J, Shimmura S, Tsubota K. Changes observed in keratolimbal allograft. Cornea. 2006; 25:377-82.
73. Meallet M, Espana E, Grueterich M, Ti S-E, Goto E, Tseng S. Amniotic membrane transplantation with conjunctival limbal autograft for total limbal stem cell deficiency. Ophthalmology. 2003; 110:1585-92.
74. Moldovan S, Borderie V, Baudrimont M, Laroche L. Treatment of unilateral limbal stem cell deficiency syndrome by limbal autograft. Journal Français Opthalmologie. 1999; 22:302-9.
75. Rauz S, Saw VP. Serum eye drops, amniotic membrane and limbal epithelial stem cells--tools in the treatment of ocular surface disease. Cell Tissue Bank. 2010; 11:13-27.
76. Schornack MM. Limbal stem cell disease: management with scleral lenses. Clin Exp Optom. 2011; 94:592-4.
77. Solomon A, Ellies P, Anderson DF, Touhami A, Grueterich M, Espana EM*, et al.* Long-term outcome of keratolimbal allograft with or without penetrating keratoplasty for total limbal stem cell deficiency. Ophthalmology. 2002; 109:1159-66.
78. Tan DTH, Ficker LA, Buckley RJ. Limbal Transplantation. Ophthalmology. 1996; 103:29-36.
79. Torres J, Fernández I, Quadrado MJ, Murta J, Herreras J, Rodríguez-Ares MT*, et al.* Limbal transplantation: multicenter retrospective case series analysis. Arch Soc Esp Oftalmol. 2008; 83:417-22.
80. Tsai RJ, Tseng SC. Human allograft limbal transplantation for corneal surface reconstruction. Cornea. 2014; 13:389-400.
81. Tsubota K, Toda I, Saito H, Shinozaki N, Shimazaki J. Reconstruction of the corneal epithelium by limbal allograft transplantation for severe ocular surface disorders. Ophthalmology. 1995; 102:1486-96.
82. Fordham R, Ciminata G, Madoni A, Magni T, Ardigo D, Pelosi D*, et al.* Cost-effectiveness analysis of ex-vivo expanded autologous corneal epithelial cells containing stem cells to repair the damaged ocular surface in patients with moderate to severe limbal stem cell deficiency due to ocular burns in the UK. Value in Health. 2015; 18 (3):A298.
83. Department of Health. NHS Reference Costs 2014 to 2015. 2015; Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.
84. Haymarket Media Group Ltd. MIMS Online2016.
85. Fielding S, Cummins E, Cruickshank M, Fraser C, Lois N, Brazzelli M. Aflibercept for treating diabetic macular oedema. 2014.
86. Beaudet A CJ, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modelling in type 2 diabetes. Value in Health. 2014; 17:462-70.
87. National Institute for Health and Care Excellence. Glaucoma: Diagnosis and management of chronic open angle glaucoma and ocular hypertension. 2009.
88. Czoski-Murray C, Carlton J, Brazier J, Young T, Papo NL, Kang HK. Valuing condition-specific health states using simulation contact lenses. Value Health. 2009; 12:793-9.
89. Finger RP, Fenwick E, Hirneiss CW, Hsueh A, Guymer RH, Lamoureux EL*, et al.* Visual impairment as a function of visual acuity in both eyes and its impact on patient reported preferences. PLoS One. 2013; 8:e81042.

90. National Institute for Health and Care Excellence. TA409: Aflibercept for treating visual impairment caused by macular oedema after branch retinal vein occlusion. 2016.
91. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Centre for Health Economics, University of York. 1999.
92. Brown MM, Brown GC, Sharma S, Busbee B. Quality of life associated with visual loss. Ophthalmology. 2003; 110:1076-81.
93. Brown MM, Brown GC, Brown HC, Irwin B, Brown KS. The comparative effectiveness and cost-effectiveness of vitreoretinal interventions. Current Opinion in Ophthalmology. 2008; 19:202-17.
94. Brown G, Brown M, Brown H, Kindermann S, Sharma S. A Value-Based Medicine Comparison of Interventions for Subfoveal Neovascular Macular Degeneration. Ophthalmology. 2007; 114:1170-8.
95. Chiesi Farmaceutici S.p.A. HOLOSIGHT: Protocol outline. 2015.
96. Chiesi Ltd. HOLOCORE-FU: Clinical Study Protocol 2015.

# 11 APPENDICES

## Appendix 1 Summary of the Kooistra criteria for a good case series

The criteria for a good case series as suggested by Kooistra[58] includes specific guidelines for planning, conducting, and reporting a case series. The criteria has been split into three sections: design, analysis and reporting and a summary of the criteria under each heading is given below:

Design

-Study question is focused and includes the following information: (1) study population, (2) the intervention and (3) the primary outcome

-inclusion and exclusion criteria should be based on widely used, preferably validated definitions. If authors use their own criteria, definition and justification are necessary to enable the reader to compare the studied population with his or her own patients.

-case series includes consecutive inclusion of patients which reduces the chance of selection bias. Use of a short inclusion period minimizes known and unknown changes over time in co-interventions, prognosis and even in the intervention under study.

-detailed description of the intervention and co-intervention should be stated. It is very important to thoroughly describe co-interventions as these are not always standardized among study centres.

-outcomes measuring patient satisfaction, symptom-relief and a feeling of well-being should be included as clinical measurements alone would not represent the subjective nature of patient care.

-the blinding of outcome assessors should be implemented as this prevents the investigators measurements from being influenced by their personal treatment preference.

-the method of data acquisition should be addressed in the study report for the sake of repeatability and the appraisal of measurement bias.

-minimal length of follow-up should be provided so that sufficient time is given for complications to develop and be recorded.

Analysis

-only descriptive statistics should be used as the design of a case series is descriptive so no comparative tests yielding p-values should be done.

Reporting

-a statement of the external validity of the obtained data should be given which includes (1) patient characteristics and (2) completeness of follow-up.

-the presence of chance and the presence, direction, and magnitude of bias should be acknowledged.

-results of prognostic variables should be provided

-follow-up rates and reasons for loss to follow-up should be stated

-no absolute conclusions on the studied treatment should be stated

**Appendix 2** Details and outcomes of the HLSTM02 and HLSTM04 case series studies.

Kooistra[58] has proposed a criteria for evaluating the design, analysis and reporting of case series which have been applied to the HLSTM02 and HLSTM04 studies. Details of the criteria can be found in Appendix 1.

**HLSTM02.** The HLSTM02 case series study is small (n=29). The critique of HLSTM02 identified that the study question is not very detailed as the study population has not been described. Full inclusion and exclusion criteria are described in the protocol and the study authors state that the same surgical procedure was followed for all patients. However, the study authors do not highlight the timeline for when patients were enrolled into the study making it difficult for the ERG to assess whether selection bias is present and whether the length of inclusion period has affected the co-interventions, prognosis or even the intervention. The study also includes only efficacy and safety outcomes but no outcomes measuring patient satisfaction or mental well-being. Relevant subjective outcomes were assessed by an independent blinded assessor highlighting that the outcomes have not been influenced by the investigators in any way. The study authors only present descriptive statistics as suggested in the criteria and do not attempt to make absolute conclusions. Overall, the ERG is of the opinion that there are a number of flaws in the design of this case series such as study question not being detailed, the length of patient enrolment period has not been stated and lack of information about patient drop outs suggesting that HLSTM02 does not seem to be a good case series.

**HLSTM04**. The HLSTM04 case series study is small (n=15). The critique of HLSTM04 identified that the study question was sufficiently detailed but the study only included efficacy and safety outcomes without measuring patient satisfaction or mental well-being. The study includes a subjective primary and a secondary outcome on symptoms that have not been assessed by an independent blinded assessor raising concern over whether the outcomes may have been influenced by the investigators. The study authors only present descriptive statistics as suggested in the criteria. The study authors do not explain reasons for patients lost to follow-up but do mention there are high levels of missing data of 60% at baseline. Overall, from critiquing the HLSTM04 study the ERG is of the opinion that this is not a good case series as subjective outcomes have not been assessed by an independent blinded assessor so could have been influenced by the investigators and there are high levels of missing data present with no reasons provided on why they are missing.

## *11.1 Quality assessment of the HLSTM02 and HLSTM04 case series studies*

The company appraised the HLSTM01, the HLSTM02 and the HLSTM04 case series studies using the Joanna Briggs Institute (JBI)[56] checklist for case series studies. The JBI checklist includes 10 items, each of which is scored as *yes*, *no*, *unclear* or *not applicable*. The company states (CS, p118) that in its assessment, a *yes* response was marked as 1, whilst all the other possible responses were marked as zero. In this way, a maximum of 10 points could be awarded per study. The company reports that the two studies scored either a 9 or a 10; this suggests that the case series studies have a low risk of bias.

However, the ERG does not completely agree with the company's assessment (see Table 40). The ERG is unclear on how the company have assessed the criteria as sufficient information has not been provided in the protocols or the CSRs for the ERG to assess whether what the company are saying is valid or not. The company has not provided data on long-term follow-up The ERG did not have sufficient information to allow an assessment of one of the JBI criteria (whether the case series had consecutive inclusion of participants). The ERG considers that the company has not provided data on long-term follow-up and has not provided details on the length of inclusion of patients into the study. Therefore, the ERG is of the opinion that the case series studies may have a greater risk of bias than the company claims.

Table 40 Company's assessment of the risk of bias for the HLSTM02 and HLSTM04 case series studies with ERG comment

| JBI checklist criteria | HLSTM02 | HLSTM04 | ERG comment |
|---|---|---|---|
| Were there clear criteria for inclusion in the case series? | 1 | 1 | Agree |
| Was the condition measured in a standard, reliable way for all participants included in the case series? | 1 | 1 | Agree |
| Were valid methods used for identification of the condition for all participants included in the case series? | 1 | 1 | Agree |
| Did the case series have consecutive inclusion of participants? | 0 | 1 | The ERG is unclear how the company has assessed this criterion as sufficient information is not provided in the protocol or CSR to assess whether the case series studies have consecutively included participants or not. |
| Did the case series have complete inclusion of participants? | 1 | 1 | Agree |
| Was there clear reporting of the demographics of the participants in the study? | 1 | 1 | Agree |
| Was there clear reporting of clinical information of the participants? | 1 | 1 | Agree |
| Were the outcomes or follow-up results of cases clearly reported? | 1 | 1 | The ERG agrees that outcomes of case series studies have been clearly reported, however long-term follow-up data have not been provided for the patients in the case series studies |
| Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | 1 | 1 | Agree |
| Was statistical analysis appropriate? | 1 | 1 | Agree |
| Score | 9 | 10 | |

CSR=clinical study report; ERG=evidence review group
Source: CS, Appendix 4

## *11.2 Study characteristics*

The study characteristics of, the HLSTM02 and the HLSTM04 case series studies are shown in Table 9.

### *11.3 Patient characteristics*

The demographic characteristics of the patients in the HLSTM02 and the HLSTM04 case series studies are presented in Table 11. Clinical advice to the ERG is that the patients in the studies are representative of patients with moderate to severe LSCD who would be treated in the NHS.

Table 41 Patient baseline characteristics in the HLSTM02 and HLSTM04 case series studies

| | **HLSTM02 N=29** | **HLSTM04 N=15** |
|---|---|---|
| Mean age (SD) | 45.8 (17.4) | 46.5 (16.9) |
| Age range | 8 to 71 | 21 to 79 |
| Male n (%) | 22 (75.9) | 14 (93) |
| Time from injury to treatment with Holoclar | 14.1 years | |

Source: CSR for HLSTM02 and HLSTM04

## 11.3.1 HLSTM02

The HLSTM02 case series study included 29 patients with a follow-up of 12 months. The primary aim of the study was to determine the safety of Holoclar in terms of the number of subjects who experienced AEs and the number of AEs. A total of 46 AEs were reported in 19 patients (65.5%). The company reports that eye disorders were the most common group of AEs. Five SAEs were reported in three patients (10.3%) and three of these SAEs in two patients were considered to be treatment-related.

A secondary endpoint in this study was the outcome of the Holoclar transplantation in terms of success or failure based on independent masked assessment. According to the independent assessor, success was achieved in 19 patients (65.5%; 95% CI: 48.2 to 82.8%), failure was reported for six patients (20.7%) and information was missing for four patients (13.8%).

## 11.3.2 HLSTM04

The primary efficacy endpoints of the study were to evaluate outcome of Holoclar transplantation, the presence and severity of clinical symptoms before and after transplant and best-refracted VA before and after treatment with Holoclar. Overall, success was reported in nine patients (60%) at the time of the 90 day follow-up and these results were maintained until the final visit (mean 217 days (85 to 777 days). Due to a large amount of data being missing at baseline (60%) it was difficult to assess the data on the presence of clinical symptoms. The results demonstrate significant improvements in VA at both day 90 and the last visit despite majority of the study population exhibiting stromal scarring.